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EJUNAL BIOPSY IN ADULT CŒLIAC DISEASE AND ALLIED DISORDERS

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> hether atrophy of the glandular crypts of the intestine be ever ays present, I cannot tell " Gee (1888)

E group of disorders giving rise to disturbance of nal absorption in the absence of gross anatomical thological changes in the gastrointestinal tract, liver, ncreas has been known by various names Cœliac se and tropical sprue have recognised clinical impli- s, but in temperate climates idiopathic steatorrhœa, opical sprue, jejunoileal insufficiency, sprue syn- e, malabsorption syndrome or just " sprue " are used for convenience than for any ætiological implication e cause of these disorders and their relation to each has been uncertain

rley (1936) believed that some cases of idiopathic steat- a were the adult form of cœliac disease and that tropical was a separate entity, while Thaysen (1932) and Bossak (1957) concluded that they were manifestations of the underlying disorder There is, however, strong clinical iochemical evidence that cœliac disease and idiopathic rrhœa, at least in some patients, are basically the same e and that tropical sprue is a separate disorder Further- as a result of the investigational techniques now available, oup known as " idiopathic steatorrhœa " seems likely to t of a number of ætiologically distinct entities In par- r a great advance was made possible by Shiner (1956) in ping a suitable method of obtaining peroral biopsies of junal mucosa with a modification of Wood's gastric suc- iopsy tube and by Crosby and Kugler (1957) with their y capsule. Ulceration, inflammation, and atrophy of the bowel mucosa had been reported in tropical and non- al sprue, but such changes were regarded as inconstant, pecific, and in any case largely due to portmortem auto- Thaysen 1932) This view was generally accepted until sberg and Schein (1947) in necropsy material, and Paul- 954) in specimens obtained at laparotomy reawakened st by demonstrating distinctive structural changes in its with " idiopathic steatorrhœa " Now, with peror y many other workers (Doniach and Shiner 1957, But- rth and Perez-Santiago 1958, Smith et al 1958, Bolt et 58, Shiner and Doniach 1959, Culver et al 1959) have nstrated definite histological abnormalities in the small ne of patients with steatorrhœa

ese observations suggest that more than one patho- al lesion may be responsible for the syndrome, but linical and ætiological signifiance of the varied find- has remained obscure In an attempt to clarify the lem, the findings in the jejunal biopsies of 58 patients " idiopathic steatorrhœa " are presented and are lated with the clinical features, the hæmatological, graphic and biochemical findings and the absorption Co vitamin B_{12}

Material and Methods

The 58 patients under discussion fulfilled the diagnostic criteria of " idiopathic steatorrhœa " (Cooke et al 1953) or " adult cœliac disease " (Cooke 1958) They have all been under regular observation for periods of from a few months to nineteen years The patients have been selected at random from those attending the steatorrhœa clinic at the General Hospital, and include all those who have been seen for the first time recently The majority of observations were made while the subjects were outpatients Biopsies have also been performed on 65 subjects of comparable age-groups—normal medical students, patients with pernicious anæmia, iron-deficiency anæmia, steatorrhœa due to pancreatic disease, regional enteritis and enterocolitis, and miscellaneous disorders not associated with gastrointestinal disease These have been used for purposes of comparison and for determining the normal structure of the jejunal mucosa

Since 1956, serum levels of vitamin B_{12} (Meynell, Cooke, Cox, and Gaddie 1957), folic-acid-excretion tests (Cox, Meynell, Cooke, and Gaddie 1958) and D-xylose-excretion tests (Fowler and Cooke 1960) have been estimated in the majority of patients

Technique

20 biopsies were performed by Dr Shiner, and these include 10 in cases of " idiopathic steatorrhœa ", the remaining 103 biopsies have been obtained with a Crosby capsule (Crosby and Kugler 1957) Fluoroscopic confirmation of the position of the capsule was obtained in all but a few patients The majority of specimens were obtained from the upper jejunum, very few from the third or fourth part of the duodenum These were fixed immediately in formol saline, embedded in paraffin, and stained with hæmatoxylin and eosin In addition, all biopsies taken with the Crosby capsule have been stained with the periodic-acid Schiff (P A S) reaction and a portion of the specimen fixed in cold acetone and stained for alkaline-phosphatase activity by the coupling azo-dye method (Pearse 195) Serial sections were examined to prevent misinterpretations due to tangential cuts through the mucosa

In 4 patients the absorption of ^{56}Co vitamin B_{12} was measured by the fæcal excretion method of Heinle et al (1952) following the oral ingestion of 0 8 μg vitamin B_{12} containing 0 5–0 85 μg ^{56}Co In the remainder the technique of surface counting over the liver (Glass 1956, 1959) was used The amount of vitamin B_{12} was 0 26–0 4 μg , containing 0 25–0 5 μC ^{58}Co and administered in 20 ml distilled water following a twelve-hour fast and immediately after an intramuscular injection of carbachol 0 25 mg (Mollin et al 1957) Surface counts were made for at least five minutes before and on two occasions between six and ten days after the administration of the test dose The resulting counts have been corrected for background radiation and decay and expressed as counts per minute per microcurie The mean in 21 control subjects was 2814 (S D 801, range 1700–4600) counts per minute per microcurie In 7 patients with pernicious anæmia, the mean was 287 (S D 141, range 0–405) counts per minute per microcurie, returning to the normal range when ^{58}Co vitamin B_{12} was administered with intrinsic factor mean 2277 (S D 473, range 1500–2979)

Results

The clinical and laboratory findings are summarised in the accompanying table and in fig 1 The histological findings in these 58 patients with " idiopathic steatorrhœa" can be classified into three groups

Group I

In 27 patients the appearances were strikingly uniform (fig 2)

The mucosa was of normal or reduced width, and the surface completely or almost completely flattened, and no normal villi were present. When present the villi appeared broad and short and tended to fuse together, elsewhere there was no suggestion of villus formation at all. Crypts of Lieberkühn were infrequent and widely spaced. The surface epithelium was grossly abnormal The cells were low cuboidal or flattened, the intercellular borders and basement membranes were indistinct, the brush border was reduced in width and frequently not visible in the hæmatoxylin and eosin (H & E), P A S, and alkaline-phosphatase preparations, the cytoplasm was often vacuolated, the nuclei varied in size, shape, and degree of staining There often numerous " nuclei " crowded together, some of which appear to be nuclear fragments and some infiltrated leucocytes while normal epithelial nuclei were infrequent. In the pits of the remaining crypts of Lieberkühn, the epithelial cells showed less abnormality, and a few mitoses could be seen There were very few goblet cells in the surface epithelial layer, although present in the tubules The glandular tubules were normal or reduced in number, and often elongated and dilated Paneth cells were present. In the lamina propria there was mild or moderately heavy cellular infiltration, consisting predominantly of plasma cells, with less numerous lymphocytes and eosinophils, a few macrophages, spindle cells, and occasional polymorph cells Some interstitial œdema and lymphatic dilatation was present

SUMMARY OF CLINICAL AND LABORATORY FINDINGS

—	Group I	Group II		
		A	B	C
Total	27	12	8	7
Age (yr) at onset	1–53	4–46	26–59	14–73
Major symptoms				
A, diarrhœa, malaise, weight loss	26	12		
B, anæmia	1		8	7
Bone-marrow				
A, megaloblastic	4	2	5	7
B, normoblastic	3	1		
Initial hæmoglobin (g per 100 ml)	7 0–16 3	10 0–14·0	4 8–7 8	3 2–10 3
Serum-vitamin-B_{12} less than 105 μμg	4 (*27*)	6 (*12*)	4 (*4*)	1 (*7*)
Vitamin-B_{12} absorption normal	16 (*18*)	5 (*7*)	1 (*6*)	6 (*6*)
Achlorhydria	4 (*13*)	4 (*7*)	6 (*6*)	0 (*7*)
Steatorrhœa	27	12	8	5 (*7*)
Xylose absorption abnormal	10 (*10*)	4 (*7*)	3 (*4*)	6 (*7*)
Folic-acid-excretion test abnormal	15 (*15*)	7 (*7*)	4 (*5*)	4 (*5*)
Remission induced by gluten-free diet	8 (*11*)	6 (*9*)		

Group I —Patients with " flat " jejunal biopsy

Group II —Patients with abnormal villi in jejunum A, patients in whom diarrhœa, malaise, and weight loss were the major features, B, patients in whom severe anæmia responding to vitamin B_{12} was the major feature, C, patients in whom severe anæmia responding to folic acid was the major feature

Figures in parentheses refer to the total number in whom the test was performed

Immediately beneath the epithelial layer in some areas there was a narrow band of homogeneous eosinophilic material, which tended to separate the epithelial layer from the underlying lamina In no instance was there any evidence of a hyaline band at the free surface of the cells, as was described by Schein (1947)

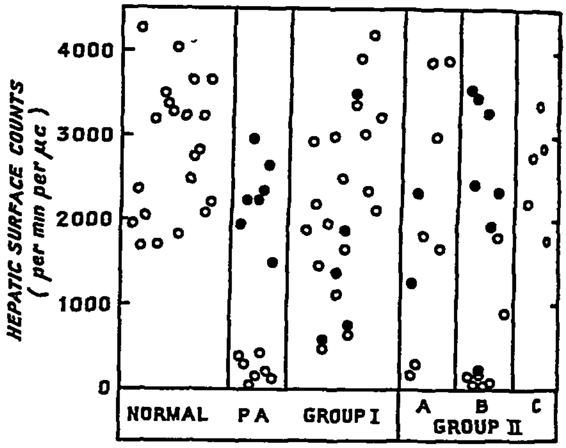


Fig 1—Absorption of radioactive vitamin B_{12}.

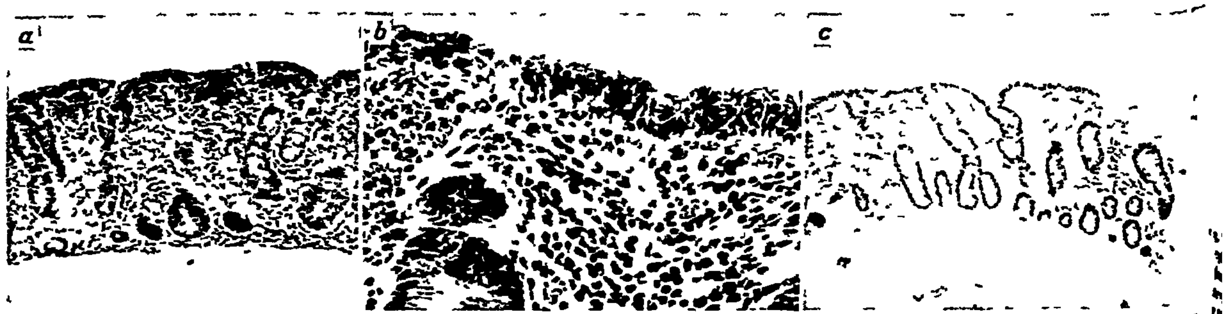
Open circles test performed with ^{58}Co vitamin B_{12}

Closed circles test performed with ^{58}Co vitamin B_{12} plus intrins factor

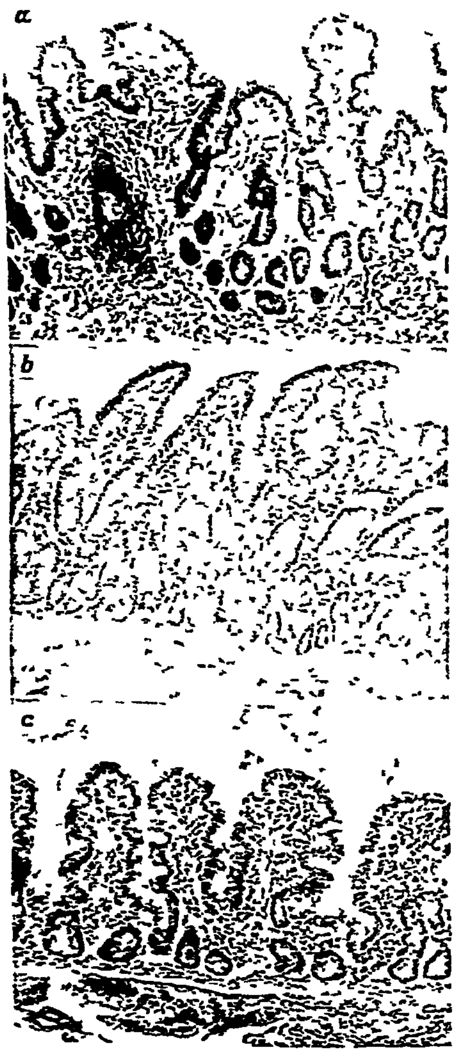
The composition of groups I and II is described in the table

Although in 11 patients biopsy was performed during clinical remission and in 16 during the initial illness or during a relapse, the histological appearance was essentially the same

The age of onset of symptoms in this group varied from early childhood to 59 years In 8, symptoms commenced before the age of 10, and in 2 others between 10 and 2 years The main presenting feature was diarrhœa, which had been present for at least two years before the patien were first seen Only in case 20, a man aged 42, could be stated that symptoms attributable to anæmia were th presenting features, there had been a severe attack o diarrhœa twelve months previously and a history o " tuberculous abdomen " at the age of 19 Glossitis a some time was common to all patients Abdominal pai however, except in the periods in which abdominal distension and hypokalæmia were present, was rare, in onl 1 patient was pain a troublesome feature and witho obvious cause The blood picture was usually macrocytic with moderate anæmia Only 7 had hæmoglob concentrations of less than 10 g per 100 ml when fir seen Although the average period of observation in th group is nearly seven years, and all have had regular blood counts, only 2 have subsequently had a hæmoglobin o less than 10 g Since severe anæmia has not been a prominent feature only 7 sternal punctures were performe Of these bone-marrows 4 were megaloblastic, the othe



g 2—Jejunal biopsy in group I (*a*) Absence of villi, flat surface, disordered epithelium, and slightly increased cellularity of la propria (case I H. & E. × 100), (*b*), epithelial surface in case 1, showing severe cellular disorder (H & E.×400), (*c*), " crypt " in 2 (serial sections suggest that these are not true crypts) (H & E. × 80) normoblastic, although 1 of these showed hyper- entation of the nuclei and giant metamyelocytes has been present in nearly all patients, and needed parenteral iron for correction Steator- varying from 8 to 25 g daily was present in all, and hic patterns of the small intestine were abnor- in all D-xylose-excretion tests were abnormal in all ested, but in 2 results were normal during subsequent Free hydrochloric acid was present in the content in 9 out of 13 in whom it was sought, in 3 of the 4 with achlorhydria histamine was not Folic-acid-excretion tests were abnormal in all 15 examined. In only 4 patients was a low serum of vitamin B_{12} encountered In 1 this was during and righted itself following confinement In her, a man aged 38 who has only recently come observation, it was associated with low levels of -iron and normal absorption of ^{58}Co vitamin B_{12} other 2 have attained normal serum levels of vitamin with treatment—1 with intramuscular iron and the with a gluten-free diet Absorption of ^{58}Co vitamin B_{12} has been studied in 18 patients In 16 absorption was normal In 2 absorption was poor and was unaltered by the addition of intrinsic factor In the only one tested, absorption was not improved by the addition of calcium Both these patients had been receiving injections of vitamin B_{12} for some time when the absorption studies were made Only 11 patients were treated with a gluten-free diet, and, of these, 3 were unable to adhere to the diet 8 patients had satisfactory clinical remissions Of the remaining 16 patients 1 died of a pulmonary infection, the others regained good health with the administration of oral folic acid or parenteral iron, often maintaining this state for years without any therapy



3—Jejunal biopsy in group II (*a*), villi abnormally shaped, epithelium only slightly abnormal, moderate cellular infiltration (case 29 H. & E × 100), (*b*), abnormally shaped villi, with less severe epithelial disorder and cellular infiltration (case 35 H. & E. ×100), (*c*), villi short and broad, surface epithelium abnormal, and cellular infiltration of lamina propria (case 40 H & E 100).

Group II

In 27 cases the microscopic appearances were considered to be abnormal (fig 3) but to differ from the appearances seen in group I In particular the absence of villi and flattening of the free surface were not found Although individual specimens showed considerable variation and so were not quite such a homogeneous histological group as group I, they did show sufficient similarities to warrant inclusion as a separate group

In a few instances the mucosa was thicker than normal, though in most it was of approximately normal or reduced width Villi were present in all specimens, but abnormal in size, shape, and structure, they were commonly short, occupying less than half the total width of the mucosa, many were broad, particularly at the base, and squat The appearance of the villi varied considerably between the individual sections, in some a few comparatively normal villi were present. The surface epithelium varied considerably in the degree of epithelial change, but this was never so severe as seen in group I, and did not always parallel the extent of abnormality of villous architecture or cellular infiltration of the lamina propria The glandular tubules showed little elongation or dilatation Goblet cells were often numerous

In the lamina propria there was mild, moderate, or heavy cellular infiltration In a few instances plasma cells were numerous, but in most the cells were mostly lymphocytes, histocytes, and spindle cells, with less numerous plasma cells, a few eosinophils, and occasional polymorphs This cellular infiltration tended to be more unevenly distributed than in group I, and was heavier in the deeper parts of the mucosa than in the villi themselves, and in some cases formed very dense follicles Often it extended into and through the muscularis mucosæ, and into the epithelium. In case 36 an area of superficial inflammatory ulceration was present

In 17 patients these changes were pronounced, with much disturbance in the architecture of the villi, moderate epithelial disorder, and moderate or heavy cellular infiltration In 10 there was less disturbance, the main features being some shortening and broadening of the villi with mild cellular infiltration

The major clinical manifestations in the patients with "abnormal villi" fell into two main categories—(1) malaise and mild diarrhœa, and (2) severe anæmia of relatively short duration. The 12 patients in whom malaise and diarrhœa were main symptoms resembled the patients with the "flat" biopsy appearance of group I, but on more detailed analysis points of difference could be demonstrated in the majority The age at onset was similar (4 to 46 years), in 3, symptoms started before the age of 10, and in 2, between 10 and 20 The duration of symptoms varied from three months to twenty years, in half it was between one and two years In 5 patients colicky abdominal pains were a feature, resulting in laparotomy in 2 In both these patients the small bowel was slightly œdematous and hyperæmic, and the mesenteric lymph-nodes were enlarged, while in 1 there were adhesions about the lower ileum Steatorrhœa was present in all Radiographically the small intestine was abnormal in all but 1 of the patients Similarly, the folic-acid-excretion test was abnormal in all except case 35, which has been reported elsewhere (Cox et al 1958) D-xylose excretion was impaired in 4 and normal in 3 Low levels of serum-iron were encountered in all but 1 Low-serum-vitamin B_{12} levels were present in 6 of the 12 patients Of these 6 patients 4 were studied with ^{58}Co vitamin B_{12} 2 had normal absorption, and in 2 the absorption was impaired but was corrected by the addition of intrinsic factor 3 further patients with normal levels of serum-vitamin-B_{12} had normal absorption of ^{58}Co vitamin B_{12} Only 3 patients (cases 29, 30, and 37) had had a hæmoglobin of less than 10 0 g per 100 ml In case 29, who had megaloblastic anæmia, complete response was effected with vitamin B_{12} Case 30 responded satisfactorily to parenteral iron Case 37, with very slight evidence of megaloblastic erythropoiesis, responded well to a gluten-free diet Of the other 2 patients in whom sternal puncture was performed, 1 had megaloblastic erythropoiesis and responded completely to injections of vitamin B_{12} Of the 7 patients in whom gastric function was investigated, 5 had no free acid in the gastric juice A gluten-free diet had been prescribed in 9 patients 6 patients improved considerably on this diet, but in some improvement could be attributed to coincident therapy with vitamin B_{12} In cases 37 and 38, however, complete clinical, hæmatological, and biochemical remission had been obtained though the folic-acid-excretion test was still abnormal in both In these 2 patients there was no detectable difference, other than the biopsy findings, from group I In case 28 no improvement resulted on a gluten-free diet for nine months, but definite improvement was subsequently obtained with steroid therapy In the other 2 patients (cases 30 and 34) improvement was noted initially In 1, final assessment is awaited, and in the other the diet was discontinued after a few months' trial with only moderate improvement, though subsequently clinical remission was attained on ordinary diet

The 15 patients presenting with severe anæmia had had symptoms for from a few weeks to a year before coming under treatment Episodes of diarrhœa had been common but relatively recent, and never as troublesome as in the other patients that have been considered Of these cases, 8 showed a prompt clinical and hæmatological response to therapy with vitamin B_{12} and only maintained this with regular treatment The ages at time of diagnosis were 26, 36, 37, 47, 50, 53, 60, and 65 years 5 of the 8 patients were seen by us before treatment, in each the bone-marrow was megaloblastic The others had already received treatment elsewhere, and the bone-marrow had not been examined The initial hæmoglobin concentration in the blood of these 5 varied from 5 to 7 g per 100 ml In the 7 patients tested, free hydrochloric acid was absent from the gastric contents In 4 of the 7 patients examined, ^{58}Co vitamin B_{12} was not absorbed normally until intrinsic factor was administered Case 40, though having a serum level of vitamin B_{12} of 75 µµg per ml , absorbed ^{58}Co vitamin B_{12} normally, and furthermore responded normally and completely to therapy with vitamin B_{12} Case 47, whose anæmia has responded well to vitamin B_{12} but in whom the initial level of serum-vitamin-B_{12} and bone-marrow appearances were not known, had subnormal absorption of ^{58}Co vitamin B_{12} The 7th patient (case 41) had severely impaired absorption which was not corrected by the addition of intrinsic factor All 7 patients tested had abnormal fæcal excretion of fat, varying from 7 to 14 g per day The folic-acid-excretion test was abnormal in 4 of the 5 patients tested, and xylose excretion was abnormal in 3 of the 4 tested

The other 7 patients responded well to folic acid or citrovorum factor In these the ages at onset were 14, 17, 32, 32, 39, 42, and 73 years 5 had steatorrhœa varying from 8 to 12 g per day, but in 2, aged 14 and 32, despite the history of diarrhœa, no steatorrhœa was demonstrated. They are included here, however, because of the abnormal xylose and folic-acid excretion tests and abnormal jejunal mucosa All had free acid in the gastric contents 6 patients when first seen had hæmoglobin concentrations of 3–7 g per 100 ml All 7 had megaloblastic bone-marrow All absorbed ^{58}Co vitamin B_{12} normally Though levels of serum-iron were within (or above) normal range at the time of their megaloblastosis, all showed evidence of iron deficiency before return to normal blood-counts 4 of the 5 patients examined had abnormal folic-acid-excretion tests The xylose-excretion test was abnormal in 4 of the 5 patients tested In the 5th (case 54) it was normal at a time when the patient was in clinical and hæmatological remission and had been under intermittent therapy for fifteen years

In none of these 15 patients presenting with anæmia was a gluten-free diet prescribed This was not necessary for control of bowel symptoms, and health and weight were rapidly regained with hæmatinics only

Group III

There were 4 patients who presented with anæmia and diarrhœa to whom the diagnosis of idiopathic steatorrhœa had been applied and in whom the jejunal biopsies had proved to be normal

3 of the 4 patients had histories of long-continued iron loss—either menorrhagia or from œsophagitis in association with a hiatus hernia In 2 steatorrhœa had been intermittently present In all, the administration of iron parenterally has led to cessation of abdominal symptoms. This group is still under investigation and will not be considered in further detail at present

Discussion

In the past few years, the functions of the various segments of the bowel have become more clearly defined. Hence, disturbances of folic-acid, xylose, and iron absorption can be expected when the jejunum is involved in disease processes, while production of the intrinsic factor fails when the gastric mucosa is atrophied Despite comments to the contrary, vitamin B_{12} is absorbed more distally, in the ileum The main site of fat absorption in the man is still debatable, for experimental observations by Bergstrom et al (1957) suggest that it takes place in the first 50–100 cm of the small intestine, whereas clinical observations in regional enteritis or following surgical resection of the gut point to the ileum as an important site of fat absorption Hence lesions of differing ætiology affecting the upper small intestine may well be associated with essentially similar clinical pictures and cause serious difficulties in differential diagnosis The converse is also true—that conditions of the same ætiology can give rise to differing clinical pictures according to the length and area of intestinal tract involved

As the result of our studies, we believe that at least two and probably three ætiologically different disorders are responsible for "idiopathic" non-tropical steatorrhœa. The most striking and homogeneous histological group series is group I, with "flat" jejunal mucosa, and consider that this represents an ætiological group from group II, in which the mucosa shows villi" Analysis of the clinical and biochemi- in the two groups seems to support this belief

might be argued that, as only single biopsies were with the Crosby capsule, such specimens are not y representative Second biopsies have been obtained only 5 patients, at an interval of at least a year after first biopsy In each case the appearances do not significantly from those in the first While repeat are being obtained in furtherance of this study, results so far seem to justify regarding the patients the "flat" biopsies as a homogeneous group, and hypothesis is unlikely to be upset by a larger number bservations

might also be argued, as Himes and Adlersberg) suggest, that the "flat" biopsies were the end- of a pathological lesion which in the earlier or less stage would have had an appearance similar to those "abnormal villi" Alternatively, if regeneration d in a "flat" mucosa, bizarre and abnormal villi ld result There does, however, appear to be strong in our patients that this is not so 3 patients in II have had the disease for fifteen to eighteen years 54 was first seen seventeen years ago with severe and has had hæmatinic therapy ever since with- ever attaining complete remission In case 30 symp- started at the age of 4, and, although she is now well the age of 22, she has had numerous severe relapses, seeking treatment when compelled to do so Case 20 had many episodes of diarrhœa and severe megalo- anæmia over a period of fifteen years and was at time of each of his two biopsies in relapse Neither nor lack of treatment appeared to have produced a lat" biopsy in these 3 patients

On the other hand, 2 patients in group I were seen , at the age of 39 and 53 with relatively mild symp- which had been present for only a year, and yet each a "flat" biopsy 6 patients in group I had been in good with no symptoms for periods of five to ten years en the biopsy was performed In 4, this was the result treatment (gluten-free diet in 3, folic acid in 1) and in of no treatment at all other than some restriction of foods All 6 have "flat" biopsies, with absence of lli and a disordered epithelium These and similar servations suggest that regeneration in this type of ion does not occur to any significant degree, although clinical remission may occur Similar observa- on the improvement in function despite the persis- of the histological changes have been made by and Doniach (1959)

The majority of published pictures and descriptions the appearances that are found in group II As yet no evidence points to transition from the abnor- villi to the biopsies with absent villi, seen in our roup-I patients Butterworth and Perez-Santiago (1958) escribed a case in which the patient had had several pisodes of severe anæmia and intermittent therapy and hich still showed abnormal villi and no "flat" biopsy at e end of nine years Butterworth and Perez-Santiago 1958) also found that in a patient with "tropical sprue" e abnormal villi returned to near normal with folic-acid erapy A similar finding had previously been reported y Shiner and Doniach (1959) The only 2 patients with opical sprue whom we have examined had had severe megaloblastic anæmia twelve to fourteen years previously and had been well without therapy for eight to ten years In both instances jejunal biopsies were essentially normal

The occurrence of virtually normal absorption of ^{58}Co vitamin B_{12}, the infrequent finding of low serum levels of vitamin B_{12}, and the relatively low incidence of severe anæmia and of severe abdominal pain are further evidence that the disorder in the patients of group I is a distinct entity The findings contrast strikingly with the findings in group II, the more so if the lesions of group II are regarded as the precursor to the development of a "flat" biopsy

Good clinical responses were obtained with a gluten-free diet in both the patients with "flat" biopsies and those with abnormal villi Since it has been suggested that "gluten-induced enteropathy" is a distinct clinical and ætiological disorder (Frazer 1959) the fact that satisfactory results were obtained in both groups could be regarded as evidence that the ætiology was the same in both despite the pathological differences There have, however, been a few case-reports of patients with secondary steatorrhœa who have been benefited by a gluten-free diet (Finlay and Wightman 1956, Forshaw 1958, Krainick 1958, Chan Jon Chu 1958, Nassim et al 1959) It cannot be deduced from this that gluten-free diet does not have a specific effect in cœliac disease, but it does apparently have a powerful non-specific effect in some intestinal disorders, and probably so acts in some patients with abnormal villi For example, in case 31 the intestinal symptoms have been satisfactorily controlled and the patient's general health improved, but even so his stools still contain 8 g of fat per day, his serum level of B_{12} is low, and intrinsic factor is absent after five years on a gluten-free diet

The pathogenesis of the lesion in group I is not known The most prominent features are the absence of villi, the disordered epithelium with evidence of cell degeneration and regeneration, and the predominantly plasma-cell infiltration of the lamina propria Evidence is accumulating that the basic defect in cœliac disease is enzymatic or cellular It has previously been suggested that such a defect in the epithelial cells would lead to all the morphological changes seen in the biopsy specimens (Himes and Adlersberg 1958) Such an explanation would be consistent with the changes seen in our group-I biopsies, but further histochemical and biochemical studies are necessary to elucidate this problem

The histological appearances in group II are less uniform than those in group I Many have the characteristics of a chronic inflammation (fig 3a) In others (fig 3b) the major change is in the appearance of the villi, with less severe epithelial disorder or cellular infiltration Whilst these latter appearances may represent a further difference in ætiology, they could well be a later or less active stage of a similar inflammatory process We therefore suggest that in many of this group the small-bowel lesion is a form of chronic jejunitis with various degrees of mucosal atrophy The findings at laparotomy in the 2 patients of this group tend to support this hypothesis of an inflammatory lesion It is noteworthy that in the only patient in group I who has had a laparotomy, the small bowel was found to be atonic and dilated, and the mesenteric lymph-nodes were not enlarged

The biopsy appearances are in general similar within each of the three subgroups of group II This does not, however, necessarily denote a common basic ætiology, indeed certain of the differences in clinical and biochemical features suggest that the distinction may not be wholly explicable simply in terms of severity or the amount of intestinal tract involved The patients whose severe megaloblastic anæmia responded to vitamin B_{12} do clearly differ from those whose anæmia responded to folic-acid substances In 4 of the former group vitamin-B_{12} absorption studies indicated a deficiency of intrinsic factor, and gastric biopsy revealed chronic atrophic gastritis in each. In those responding to folic acid, the presence of free gastric hydrochloric acid and normal absorption of ^{58}Co vitamin B_{12} indicate that the gastric mucosa is virtually normal, although histological confirmation of this has not yet been obtained It might be argued that the difference between these two groups is merely that in one the lesion is more extensive and involves the stomach as well as the jejunum If this were so, however, one should expect to find that the vitamin-B_{12}-deficient group would also manifest folic-acid deficiency, but this has not been the case It is also of interest that one of the patients whose anæmia responded to vitamin B_{12} had a normal absorption of ^{58}Co vitamin B_{12} In this patient (case 40), a man of 39, gastric biopsy revealed normal mucosa The mechanism of the vitamin-B_{12} deficiency in this case is not yet clear, it is certainly different from the other patients in this group, and further study may reveal that the basic ætiology is also different The patients with vitamin-B_{12} deficiency and intrinsic factor defect must also cause difficulty in differentiation from addisonian pernicious anæmia unless intestinal absorption studies and jejunal biopsies are performed Similar examples of steatorrhœa and lack of intrinsic factor, though without biopsy studies, have been recorded by Mollin et al (1957), Jarvinen and Latvalahti (1958), and Williams et al (1958)

Jejunal-biopsy appearances essentially similar to those which we have described in group I have been described in cœliac disease (Sakula and Shiner 1957, Brandborg et al 1959) Rubin et al (1958) believe that the findings in cœliac disease and "idiopathic sprue" are identical, basing their opinion on 9 juvenile cœliacs and 17 adult patients At the Children's Hospital, Birmingham, biopsies have been performed on 26 children with steatorrhœa aged 2–14 years 24 who had the clinical features of cœliac disease had histological findings similar to those described in our group I (Cameron 1960) We suggest that in future the name cœliac disease or adult cœliac disease should be applied only to those patients with a "flat" jejunal biopsy For the moment, there is no suitable designation for those with "abnormal villi", though "jejunitis", "non-tropical sprue", or simply "sprue" may each have its advocates

Of the patients with "flat" biopsies and those with abnormal villi, a few failed to absorb vitamin B_{12} even with the addition of intrinsic factor Oxenhorn et al (1958) found that this was so in nearly all the 25 patients that they studied As was suggested by Mollin et al (1959) this failure to absorb vitamin B_{12} with the addition of intrinsic factor should indicate extension of the lesions down the intestinal tract Such lesions have been reported by Thaysen (1932), Salvesen and Skogrand (1957), Mollin et al (1959), and Shiner and Doniach (1959), but there has been little published evidence on the frequency of normal microscopic appearances in the ileum With the reservations necessary when dealing with postmortem findings, we believe that the distal small intestine in some of our cases [illegible]ed at necropsy was normal, as was suggested in the present series by our findings with ^{58}Co vitamin B_{12} Furthermore, since similar findings with regard to absorption of vitamin B_{12} occur in regional enteritis, the fact that such findings are also encountered in both the patients with "flat" biopsies and those with abnormal villi does not necessarily signify that the two groups are ætiologically identical

The apparent dissociation between the absorption of vitamin B_{12} and fat in the patients with "flat" biopsies and in those with the abnormal villi and megaloblastic anæmias responding to folic acid is not readily explained, but possibly the observation of Borgstrom et al (1958) that fat is absorbed in the first 50–100 cm of the small intestine is relevant Nevertheless, it might have been expected that the lower ileum would take over fat absorption, since in regional enteritis excision of the lower ileum often leads to steatorrhœa

Summary

Jejunal biopsies have been performed on patients with "*idiopathic steatorrhœa*" or "*adult cœliac disease*"

In 27 patients the appearances were uniform, with absent villi, epithelial disorder, and mild to moderate cellular infiltration, mainly with plasma cells

In 27 the villi were present but abnormal in shape, the epithelial disturbance was less severe, and the cellular infiltration was usually heavier

In 4 patients the villi were normal

Clinical features and laboratory findings indicate that the cases with absent villi are ætiologically distinct from the rest It is suggested that this group be called cœliac disease or adult cœliac disease, and that these terms be confined to patients with this lesion

The second group with abnormal villi probably represents more than one ætiological disorder For this group there is at present no satisfactory name

We are grateful to Dr M Shiner for introducing us to jejunal biopsy and for allowing us to include the results thus obtained, the physicians of the General Hospital for allowing us to investigate their patients, and Dr C F Hawkins for referring cases 29-32 for further study, and lastly, but by no means least, to the many patients who willingly gave their time to allow these investigations to be carried out We are indebted to the endowment research fund of the United Birmingham Hospitals for a grant for equipment and for financial support to one of us

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ITIS AND CIRRHOSIS OF LIVER

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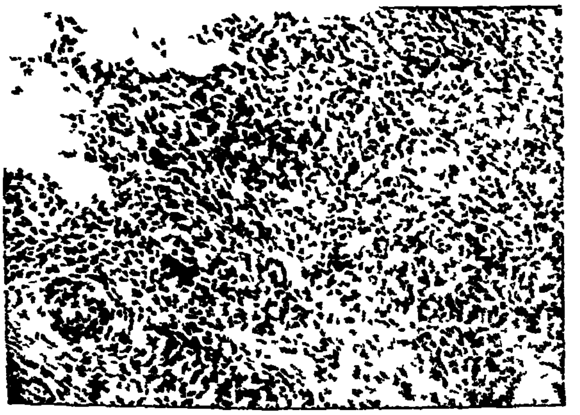
question whether thyroiditis may be associated cirrhosis of the liver has been widely discussed and Cooke 1956, Roitt and Doniach 1958, ierson et al 1959a and b, Doniach et al 1959) but very patients with both diseases have been described e present three instances of death from liver failure who had chronic thyroiditis

Case-reports

1 —A married woman, born in 1903, had had jaundice 911 but otherwise had been healthy until 1954 when she the Cardiff Royal Infirmary because of a swelling in neck. She remembered that she had had a goitre for some between the ages of 10 and 19 This had gradually ided, but six months before being seen in hospital she had



1—Case 1 microscopic appearance of thyroid gland (×100)

oticed a return of the swelling and it was gradually increasing size There were no other symptoms

The patient was of normal build without any evidence of or thyrotoxicosis Abnormal physical findings confined to the neck where there was diffuse firm enlarge- of the thyroid gland, particularly on the right side (B P) 145/90 mm Hg Hb 10 6 g per 100 ml , cholesterol 345 mg per 100 ml She was admitted to , and on Aug 6, 1954, subtotal thyroidectomy was by Mr D B E Foster The appearance of the at operation suggested chronic thyroiditis of Hashimoto's , and the histological report (Dr A. G Heppleston) was the features are those of Hashimoto's disease with considerable squamous metaplasia of the surviving epithelium" (fig 1) Recovery from the operation was uneventful, and the patient was given thyroid extract gr 1 daily

She was next seen at the Cardiff Royal Infirmary in 1957 She had had epigastric pain for three years, and loose pale motions and jaundice for six months The urine had been dark. Jaundice had varied in intensity and was not very noticeable when she was examined No thyroid tissue could be seen or felt There were spider nævi on both hands and one on the face, and there were bruises on the legs The liver was enlarged to 2 in below the costal margin and was not tender, the spleen was palpable. There was no œdema or ascites *B P 130/75*

The blood-count was normal (Hb 11 8 g per 100 ml , white cells 4900 per c.mm) but the erythrocyte-sedimentation rate (E S R) was raised (43 mm in the first hour, Wintrobe) Serum-protein 7 6 g (albumin 2 9 g) per 100 ml , electrophoretic pattern showed increased γ-globulin Serum-bilirubin 2 5 mg per 100 ml , serum-alkaline-phosphatase 25 2 King-Armstrong (K -A) units per 100 ml Thymol turbidity 20 units and thymol flocculation 4+

During the latter half of 1957 the patient's condition did not change, but in 1958 the jaundice increased and she began to feel unwell In view of this and the possibility that Hashimoto's disease might be related to cirrhosis it was decided to seek the opinion of Dr Sheila Sherlock The patient was transferred to

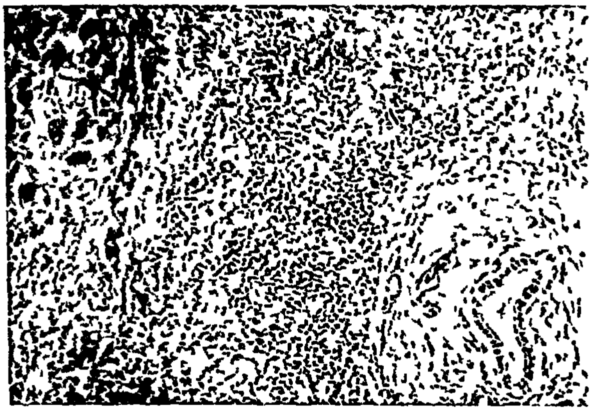


Fig 2—Case 1 microscopic appearance of liver (×100)

the Hammersmith Hospital and we are indebted to Professor Sherlock for the results of the following additional investigations

Liver biopsy fibrosis, some distortion of pattern, cirrhosis, liver cells swollen, vacuolated, and bilestained, portal tracts heavily infiltrated with lymphocytes—an active cirrhosis Thyroglobulin precipitin test positive Complement-fixation strong positive Tanned-red-cell agglutination strong positive Radio-iodine test "T" factor 1 6 (normal 2 8—13)

While at Hammersmith Hospital the patient was given prednisolone, but this was stopped because she felt unwell and œdema developed She was then given triamcinolone 4 mg b d and went home two weeks later

Three months later, in November, 1958, she was readmitted to the Cardiff Royal Infirmary She felt extremely unwell and had had œdema of the ankles continuously A month before readmission the jaundice had become worse, her abdomen began to swell and she developed diarrhœa, a sore mouth, and dyspnœa on exertion During this month she had had no further triamcinolone She had been having a high-protein, low-salt diet, mersalyl twice weekly, and thyroid extract gr 1 twice daily

The patient looked thin and ill and was deeply jaundiced There was œdema of the legs and over the sacrum, there was also severe ascites, and the liver and spleen were enlarged.

The serum-protein was now 6 0 g (albumin 1 6 g) per 100 ml , serum-alkaline-phosphatase 34 K.-A. units per 100 ml , and serum-bilirubin 14 3 mg per 100 ml Thymol turbidity

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7 units and thymol flocculation 2+. Serum-electrolytes were normal (sodium 137 mEq., potassium 3.3 mEq., and chloride 103 mEq. per litre).

Three days after admission the patient became drowsy and had severe diarrhœa. This continued and her condition deteriorated gradually. She became comatose on the fourteenth day after admission and died two days later.

Postmortem Findings

The peritoneal cavity contained a large amount of ascitic fluid, and the intestinal tract contained much altered blood originating from œsophageal varices. No recognisable thyroid tissue was found, and the fragments of tissue taken for section consisted only of lymphoid and fibrous tissue. The liver weighed 1100 g., was of firm consistence, and was traversed by a network of grey fibrous tissue in which were embedded greenish nodules of liver tissue. Histologically (fig. 2) there was diffuse fibrosis with nodular hyperplasia of liver parenchyma. The fibrous tissue showed widespread and intense infiltration with plasma cells and lymphocytes. Bile-duct proliferation was present round the periphery of most nodules, and intracanalicular bile thrombi were present.

Case 2.—A married woman, born in 1901, had diphtheria when she was a child, and in 1927 both her ovaries were removed because of persistent abdominal pain two years after the birth of a child.

In 1938 she noticed that her abdomen had become swollen quite suddenly. Soon after this her limbs and face became puffy and she gained weight. At the same time she noticed that her urine was frothy and scanty. She was admitted to hospital where subacute nephritis was diagnosed (no notes are available for this admission). At the time of discharge she was still œdematous, and this œdema persisted, varying in degree.

In 1949 she began to have attacks of angina pectoris. These increased in severity and duration and led to her admission to hospital in 1952. At that time she was noted to be pale, obese, and œdematous. The ankles and face were puffy and the eyebrows scanty. The skin was thick, dry, and pigmented and the nails were brittle. There were numerous bruises on the skin. The thyroid was not enlarged, nor were the liver or spleen palpable. B.P. 210/130.

The basal metabolic-rate (B.M.R.) was −20%, and serum-cholesterol 450 mg. per 100 ml. A radiograph of the chest showed that the heart was enlarged and an electrocardiograph, which was of normal voltage, showed left axis deviation and myocardial ischæmia. Serum-protein 7.6 g. (albumin 4.7 g.) per 100 ml. The urine contained no protein or abnormal deposit.

Myxœdema with coronary atherosclerosis was diagnosed, and the patient was given thyroid extract gr. $^{1}/_{10}$ daily, which was gradually increased to gr. 1 t.d.s. She improved rapidly at first, but a month after admission had a coronary occlusion which was followed by mild heart-failure. Treatment with thyroid extract was interrupted for three weeks and then resumed with gr. $^{1}/_{10}$ daily which was increased to gr. 1 q.d.s. After being in hospital for four months the patient went home feeling much better. She then had no œdema, and had lost 3 st. in weight. B.M.R. +10%. Serum-cholesterol 270 mg. per 100 ml.

Her condition improved gradually until December, 1952, when she began to have attacks of epigastric pain followed by vomiting. These occurred at night and were accompanied by a desire to defæcate. In January, 1953, she became jaundiced and noticed increasing thirst. Her urine was dark and motions pale. Despite a return of the ankle œdema she began to lose weight rapidly. She was readmitted on Jan. 30, 1953.

The patient was found to be jaundiced and lethargic. Her face was puffy but there was no œdema elsewhere. The liver was enlarged to 5 in. below the costal margin, but the spleen was not palpable. B.P. 105/50.

Serum-protein 7.3 g. (albumin 3.7 g.) per 100 ml., serum-alkaline-phosphatase 34.2 K.-A. units per 100 ml., serum-bilirubin 21.6 mg. per 100 ml., thymol turbidity 1 unit, thymol flocculation 0, zinc turbidity (Kunkel) 4 units, prothrombin index 1.6. The blood-count was normal (Hb 13.4 g. per 100 ml., white cells 9000 per c.mm.), and serum-cholesterol 295 mg. per 100 ml.

Condition deteriorated rapidly and within three days it was apparent that her liver was decreasing rapidly in size. Jaundice increased and six days after admission she became comatose and died.

Postmortem Findings

There were ulcerated œsophageal varices, and the gastrointestinal tract contained a considerable amount of altered blood. The liver weighed 1780 g. and was finely granular. Microscopically the appearance of the liver closely resembled that in case 1 except that the infiltration of the fibrous tissue with lymphoid cells was less intense and some eosinophil leucocytes were present. There was no necrosis of liver parenchyma. The thyroid gland consisted of a network of fibrous tissue in which were embedded nodules of thyroid parenchyma. These were composed of small acini lined by eosinophilic and pleomorphic cells. There was little colloid in evidence. Extensive accumulations of lymphocytes and plasma cells surrounded and infiltrated the nodules. The appearances were those of chronic thyroiditis of Hashimoto type.

Case 3.—A married woman, born in 1892, had been healthy until February, 1948, when she had a small hæmatemesis. In September, 1948, she had three further hæmatemeses and had to be admitted to hospital. She was pale and shocked. B.P. 100/60, pulse-rate 100 per min. Abnormal physical signs were confined to the abdomen; her spleen was enlarged. After blood-transfusion her condition rapidly improved, and she then said that she thought she had had hæmatemeses in about 1917 and 1923. Radiographic examination showed that she had œsophageal varices. Liver-function tests were substantially normal (serum-protein 7.5 g. (albumin 4.5 g.) per 100 ml., serum-bilirubin 0.5 mg. per 100 ml., serum-alkaline-phosphatase 12 K.-A. units per 100 ml., thymol turbidity 6 units).

In 1952 the patient again had a hæmatemesis and was readmitted to hospital. There was no comment on the thyroid gland, but her spleen was still enlarged. Liver-function tests were repeated with results similar to those found in 1948.

She then remained well until June, 1955, when she was again admitted to hospital having had three hæmatemeses. On examination she was obese and pale but not shocked. Her appearance was "heavy, with impression of myxœdema or nephrotic facies." The skin was dusky; jaundice was suspected but not definite. The thyroid gland was not enlarged. The liver was not palpable but the spleen was enlarged. There was no ascites.

The patient was anæmic (Hb 9.9 g. per 100 ml.) and the blood-urea was 158 mg. per 100 ml. The serum-bilirubin was 10.7 mg. per 100 ml., serum-alkaline-phosphatase 6.5 K.-A. units per 100 ml., thymol turbidity 1 unit, thymol flocculation 0, prothrombin index 1.5.

Later on the day of admission the patient had two more hæmatemeses and became drowsy. A transfusion of whole blood was begun. Next day she was still drowsy and jaundice was now obvious. She had further hæmatemeses and the transfusion was continued. She was also given chlortetracycline orally (500 mg. six-hourly). Despite repeated transfusion her Hb fell from 69% on admission to 27% five days later, and she died on the sixth day having been comatose for twenty-four hours.

Postmortem Findings

The liver weighed 720 g., and the cut surface showed deeply jaundiced areas of surviving liver tissue embedded in a deep red stroma. Microscopically there was widespread massive necrosis of liver parenchyma, and in many areas the liver cell had disappeared altogether leaving only stromal elements. There was some increase of periportal connective tissue, which was patchily infiltrated with plasma and lymphoid cells and ich proliferation of bile-ducts was discernible. The thy-d gland was small and fibrous Histologically it consisted fibro-fatty tissue in which were small islands of thyroid ue surrounded by dense accumulations of plasma cells lymphocytes The thyroid tissue showed recent acute , and no colloid containing alveoli were seen

each of these three cases, in which chronic thyroiditis diffuse hepatic fibrosis were associated, the patient a postmenopausal woman.

In the first a subtotal thyroidectomy had been carried , on account of Hashimoto's disease, four years before death from liver failure, this patient had had jaundice she was 8 years old In the second there had been ical evidence of myxœdema for at least ten years before from liver failure. In the third chronic thyroiditis found incidentally at postmortem examination owing death due to hæmorrhage from œsophageal ces and liver failure.

The striking feature of the histological examinations the thyroids and livers from these patients was the larity between the changes in the two organs in oth organs there were loss of the normal pattern, fibrosis, collections of lymphocytes and plasma cells In one (case 3) there was acute necrosis in both the d and the liver

Discussion

Cases of coexisting thyroiditis and cirrhosis have been eported before. Thus Luxton and Cooke (1956) scribed two cases of diffuse hepatic fibrosis with al evidence of Hashimoto's disease, and Roitt and oniach (1958) mentioned four cases of chronic thyroid- with unspecified liver diseases, in one of these liver iopsy showed periportal lymphoid infiltration and is The finding by Goudie et al (1959) that the of elderly women with cirrhosis contain anti-thyroid odies significantly more often than the sera of nts with other diseases, and reports that the sera of me patients (about 8% [Doniach et al 1959]) with ashimoto's disease absorb complement in the presence of liver and other organs (Roitt and Doniach 1958, Anderson et al. 1959a and b), have also been taken to dicate an association between cirrhosis and thyroiditis In our patients the histological appearances in the thyroid glands and the liver were strikingly similar including, in one case, the presence of necrosis in both organs

The histological features we have described in the thyroid glands are similar to those reported in patients with chronic thyroiditis in whom anti-thyroid antibodies have been demonstrated (*Lancet* 1958, 1959, *Scot med J* 1959, Smart 1959); indeed in one of our patients such antibodies were shown The histological appearances in the livers, resembling as they do those in the thyroids, suggest to us a similar basis There is in fact evidence that antibodies reacting with liver are present in the serum of some patients with diffuse hepatic fibrosis (Gajdusek 1958, Mackay and Gajdusek 1958)

A relationship between thyroiditis and diffuse hepatic fibrosis might be no more than a particular example of associations that have been postulated to exist between a number of disorders in which autoimmune mechanisms may be implicated (see Doniach et al 1959) The thyroid gland is not always sectioned in cases where the patient has died of liver failure, but it would be clearly worth while to obtain more information on the histology of the thyroid in such patients A study of the association between chronic thyroiditis and diffuse hepatic fibrosis might well throw further light on the ætiology of both Whether autoimmunity initiates the disease in both organs, or whether it develops as the result of a disorder affecting both organs more or less simultaneously, cannot be said. Finally there remains the possibility that disease in one organ is the consequence of disease in the other, if that were so our clinical evidence suggests that the thyroiditis precedes the hepatic fibrosis

Summary

Three postmenopausal women who died of liver failure all had chronic thyroiditis, in two of them this was the original presenting feature, but in the third it was found incidentally The histological findings in the liver and thyroid glands were similar, consisting in disappearance of the normal pattern, fibrosis, and infiltration with lymphocytes and plasma cells

An association between chronic thyroiditis and diffuse hepatic fibrosis is therefore suggested If such could be established it might be regarded as another example of association between diseases in which autoimmune processes are involved

We wish to thank Dr W Phillips and Dr I G Jones for permission to publish these cases, Prof H Scarborough, Prof J Gough, Dr Paul Fourman, and Dr H J Whiteley for helpful advice, and Mr M H Travers for the photographs

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FAMILIAL GLOMERULONEPHRITIS AND AMINOACIDURIA

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MANY examples of familial nephritis have been reported (Mitchell 1930, Rinkoff et al. 1939, Tudor 1943, Perkoff et al 1951, 1958, Sohar 1956, Sturtz and Burke 1956, Goldbloom et al 1957) Osman (1927) stated that in 11% of all cases of nephritis there was a family history of renal disease. Familial nephrosis has been described by Vernier et al. (1957), and familial renal sclerosis by Clark (1951)

We describe here an example of familial glomerulonephritis associated with a metabolic renal abnormality

Affected Family

In a family of 8 (fig 1) 3 children (cases 1–3) died as a result of chronic glomerulonephritis, a 4th child died in infancy, the cause being unknown

Case 1—In December, 1954, when 12 years old, Barbara, although symptom-free, was found to have proteinuria and mild hypertension, "chronic nephritis with a good reserve of renal function" was diagnosed. In May, 1956, when her brother developed renal disease, she was more fully investigated. A blood-pressure of 135/90 mm Hg was the only

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7 units and thymol flocculation 2+ Serum-electrolytes were normal (sodium 137 mEq , potassium 3 3 mEq , and chloride 103 mEq per litre)

Three days after admission the patient became drowsy and had severe diarrhœa This continued and her condition deteriorated gradually She became comatose on the fourteenth day after admission and died two days later

Postmortem Findings

The peritoneal cavity contained a large amount of ascitic fluid, and the intestinal tract contained much altered blood originating from œsophageal varices No recognisable thyroid tissue was found, and the fragments of tissue taken for section consisted only of lymphoid and fibrous tissue The liver weighed 1100 g , was of firm consistence, and was traversed by a network of grey fibrous tissue in which were embedded greenish nodules of liver tissue Histologically (fig 2) there was diffuse fibrosis with nodular hyperplasia of liver parenchyma The fibrous tissue showed widespread and intense infiltration with plasma cells and lymphocytes Bile-duct proliferation was present round the periphery of most nodules, and intracanalicular bile thrombi were present

Case 2 —A married woman, born in 1901, had diphtheria when she was a child, and in 1927 both her ovaries were removed because of persistent abdominal pain two years after the birth of a child

In 1938 she noticed that her abdomen had become swollen quite suddenly Soon after this her limbs and face became puffy and she gained weight At the same time she noticed that her urine was frothy and scanty She was admitted to hospital where subacute nephritis was diagnosed (no notes are available for this admission) At the time of discharge she was still œdematous, and this œdema persisted, varying in degree

In 1949 she began to have attacks of angina pectoris These increased in severity and duration and led to her admission to hospital in 1952 At that time she was noted to be pale, obese, and œdematous The ankles and face were puffy and the eyebrows scanty The skin was thick, dry, and pigmented and the nails were brittle There were numerous bruises on the skin The thyroid was not enlarged, nor were the liver or spleen palpable B P 210/130

The basal metabolic-rate (B M R) was −20%, and serum-cholesterol 450 mg per 100 ml A radiograph of the chest showed that the heart was enlarged and an electrocardiograph, which was of normal voltage, showed left axis deviation and myocardial ischæmia Serum-protein 7 6 g (albumin 4 7 g) per 100 ml The urine contained no protein or abnormal deposit

Myxœdema with coronary atherosclerosis was diagnosed, and the patient was given thyroid extract gr $^1/_{10}$ daily, which was gradually increased to gr 1 t d s She improved rapidly at first, but a month after admission had a coronary occlusion which was followed by mild heart-failure Treatment with thyroid extract was interrupted for three weeks and then resumed with gr $^1/_{10}$ daily which was increased to gr 1 q d s After being in hospital for four months the patient went home feeling much better She then had no œdema, and had lost 3 st in weight B.M R. +10% Serum-cholesterol 279 mg per 100 ml

Her condition improved gradually until December, 1952, when she began to have attacks of epigastric pain followed by vomiting These occurred at night and were accompanied by a desire to defæcate In January, 1953, she became jaundiced and noticed increasing thirst Her urine was dark and motions pale Despite a return of the ankle œdema she began to lose weight rapidly She was readmitted on Jan 30, 1953

The patient was found to be jaundiced and lethargic Her face was puffy but there was no œdema elsewhere The liver was enlarged to 5 in below the costal margin, but the spleen was not palpable B P 105/50

Serum-protein 7 3 g (albumin 3 7 g) per 100 ml , serum-alkaline-phosphatase 34 2 K -A units per 100 ml , serum-bilirubin 21 6 mg per 100 ml , thymol turbidity 1 unit, thymol flocculation 0, zinc turbidity (Kunkel) 4 units, prothrombin index 1 6 The blood-count was normal (Hb 13 4 g per 100 ml , white cells 9000 per c mm), and serum-cholesterol 295 mg per 100 ml

Condition deteriorated rapidly and within three days it was apparent that her liver was decreasing rapidly in size Jaundice increased and six days after admission she became comatose and died

Postmortem Findings

There were ulcerated œsophageal varices, and the gastrointestinal tract contained a considerable amount of altered blood The liver weighed 1780 g and was finely granular Microscopically the appearance of the liver closely resembled that in case 1 except that the infiltration of the fibrous tissue with lymphoid cells was less intense and some eosinophil leucocytes were present. There was no necrosis of liver parenchyma The thyroid gland consisted of a network of fibrous tissue in which were embedded nodules of thyroid parenchyma These were composed of small acini lined by eosinophilic and pleomorphic cells There was little colloid in evidence Extensive accumulations of lymphocytes and plasma cells surrounded and infiltrated the nodules The appearances were those of chronic thyroiditis of Hashimoto type

Case 3 —A married woman, born in 1892, had been healthy until February, 1948, when she had a small hæmatemesis In September, 1948, she had three further hæmatemeses and had to be admitted to hospital She was pale and shocked B P 100/60, pulse-rate 100 per min Abnormal physical signs were confined to the abdomen, her spleen was enlarged After blood-transfusion her condition rapidly improved, and she then said that she thought she had had hæmatemeses in about 1917 and 1923 Radiographic examination showed that she had œsophageal varices Liver-function tests were substantially normal (serum-protein 7 5 g (albumin 4 5 g) per 100 ml , serum-bilirubin 0 5 mg per 100 ml , serum-alkaline-phosphatase 12 K -A units per 100 ml , thymol turbidity 6 units)

In 1952 the patient again had a hæmatemesis and was readmitted to hospital There was no comment on the thyroid gland, but her spleen was still enlarged Liver-function tests were repeated with results similar to those found in 1948

She then remained well until June, 1955, when she was again admitted to hospital having had three hæmatemeses On examination she was obese and pale but not shocked Her appearance was “ heavy, with impression of myxœdema or nephrotic facies ” The skin was dusky, jaundice was suspected but not definite The thyroid gland was not enlarged. The liver was not palpable but the spleen was enlarged There was no ascites

The patient was anæmic (Hb 9 9 g per 100 ml) and the blood-urea was 158 mg per 100 ml The serum-bilirubin was 10 7 mg per 100 ml , serum-alkaline-phosphatase 6 5 K -A units per 100 ml , thymol turbidity 1 unit, thymol flocculation 0, prothrombin index 1 5

Later on the day of admission the patient had two more hæmatemeses and became drowsy A transfusion of whole blood was begun Next day she was still drowsy and jaundice was now obvious She had further hæmatemeses and the transfusion was continued She was also given chlortetracycline orally (500 mg six-hourly) Despite repeated transfusion her Hb fell from 69% on admission to 27% five days later, and she died on the sixth day having been comatose for twenty-four hours

Postmortem Findings

The liver weighed 720 g , and the cut surface showed deeply jaundiced areas of surviving liver tissue embedded in a deep red stroma Microscopically there was widespread massive necrosis of liver parenchyma, and in many areas the liver cell had disappeared altogether leaving only stromal elements There was some increase of periportal connective tissue, which was patchily infiltrated with plasma and lymphoid cells and which proliferation of bile-ducts was discernible The thy- gland was small and fibrous Histologically it consisted fibro-fatty tissue in which were small islands of thyroid ue surrounded by dense accumulations of plasma cells lymphocytes The thyroid tissue showed recent acute sis, and no colloid containing alveoli were seen

each of these three cases, in which chronic thyroiditis diffuse hepatic fibrosis were associated, the patient a postmenopausal woman

In the first a subtotal thyroidectomy had been carried , on account of Hashimoto's disease, four years before death from liver failure, this patient had had jaundice she was 8 years old In the second there had been nical evidence of myxœdema for at least ten years before from liver failure In the third chronic thyroiditis as found incidentally at postmortem examination llowing death due to hæmorrhage from œsophageal and liver failure.

The striking feature of the histological examinations the thyroids and livers from these patients was the between the changes in the two organs in oth organs there were loss of the normal pattern, fibrosis, d collections of lymphocytes and plasma cells In one (case 3) there was acute necrosis in both the and the liver

Discussion

Cases of coexisting thyroiditis and cirrhosis have been orted before Thus Luxton and Cooke (1956) ed two cases of diffuse hepatic fibrosis with evidence of Hashimoto's disease, and Roitt and (1958) mentioned four cases of chronic thyroid- tis with unspecified liver diseases, in one of these liver opsy showed periportal lymphoid infiltration and The finding by Goudie et al (1959) that the era of elderly women with cirrhosis contain anti-thyroid es significantly more often than the sera of with other diseases, and reports that the sera of patients (about 8% [Doniach et al 1959]) with Hashimoto's disease absorb complement in the presence of liver and other organs (Roitt and Doniach 1958, A et al 1959a and b), have also been taken to cate an association between cirrhosis and thyroiditis In our patients the histological appearances in the thyroid glands and the liver were strikingly similar including, in one case, the presence of necrosis in both organs

The histological features we have described in the thyroid glands are similar to those reported in patients with chronic thyroiditis in whom anti-thyroid antibodies have been demonstrated (*Lancet* 1958, 1959, *Scot med J* 1959, Smart 1959), indeed in one of our patients such antibodies were shown The histological appearances in the livers, resembling as they do those in the thyroids, suggest to us a similar basis There is in fact evidence that antibodies reacting with liver are present in the serum of some patients with diffuse hepatic fibrosis (Gajdusek 1958, Mackay and Gajdusek 1958)

A relationship between thyroiditis and diffuse hepatic fibrosis might be no more than a particular example of associations that have been postulated to exist between a number of disorders in which autoimmune mechanisms may be implicated (see Doniach et al 1959) The thyroid gland is not always sectioned in cases where the patient has died of liver failure, but it would be clearly worth while to obtain more information on the histology of the thyroid in such patients A study of the association between chronic thyroiditis and diffuse hepatic fibrosis might well throw further light on the ætiology of both Whether autoimmunity initiates the disease in both organs, or whether it develops as the result of a disorder affecting both organs more or less simultaneously, cannot be said Finally there remains the possibility that disease in one organ is the consequence of disease in the other, if that were so our clinical evidence suggests that the thyroiditis precedes the hepatic fibrosis

Summary

Three postmenopausal women who died of liver failure all had chronic thyroiditis, in two of them this was the original presenting feature, but in the third it was found incidentally The histological findings in the liver and thyroid glands were similar, consisting in disappearance of the normal pattern, fibrosis, and infiltration with lymphocytes and plasma cells

An association between chronic thyroiditis and diffuse hepatic fibrosis is therefore suggested If such could be established it might be regarded as another example of association between diseases in which autoimmune processes are involved

We wish to thank Dr W Phillips and Dr I G Jones for permission to publish these cases, Prof H Scarborough, Prof J Gough, Dr Paul Fourman, and Dr H J Whiteley for helpful advice, and Mr M H Travers for the photographs

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FAMILIAL GLOMERULONEPHRITIS AND AMINOACIDURIA

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Many examples of familial nephritis have been reported (Mitchell 1930, Rinkoff et al 1939, Tudor 1943, Perkoff et al 1951, 1958, Sohar 1956, Sturtz and Burke 1956, Goldbloom et al 1957) Osman (1927) stated that in 11% of all cases of nephritis there was a family history of renal disease Familial nephrosis has been described by Vernier et al (1957), and familial renal sclerosis by Clark (1951)

We describe here an example of familial glomerulonephritis associated with a metabolic renal abnormality

Affected Family

In a family of 8 (fig 1) 3 children (cases 1–3) died as a result of chronic glomerulonephritis, a 4th child died in infancy, the cause being unknown

Case 1—In December, 1954, when 12 years old, Barbara, although symptom-free, was found to have proteinuria and mild hypertension, " chronic nephritis with a good reserve of renal function " was diagnosed In May, 1956, when her brother developed renal disease, she was more fully investigated. A blood-pressure of 135/90 mm Hg was the only

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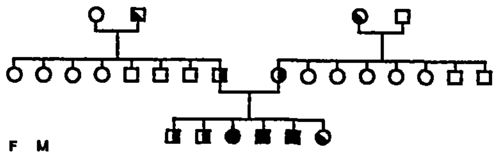


○ □ Females and males data incomplete, but no gross renal disease
◨ Aminoaciduria
◪ Died from other causes
■ Died from glomerulonephritis

Fig 1—Family tree

abnormal finding on clinical examination Urinalysis revealed proteinuria, with a few red blood-cells and granular casts, hæmoglobin 16 3 g per 100 ml, erythrocyte-sedimentation rate (E S R) 13 mm in the first hour (Westergren), blood-urea 26 mg per 100 ml, serum-cholesterol 300 mg per 100 ml, serum-proteins 6 6 g (albumin 4 2 g, globulin 2 4 g) per 100 ml Serum electrophoresis showed an increase in α_2-globulin Urinary aminoacid chromatography showed pronounced generalised aminoaciduria, identical with that in other members of this family, and excretion of the nephrosis peptide Chronic nephrotic nephritis was diagnosed, but treatment with cortisone did not control the proteinuria

In July, 1956, an adequate percutaneous renal biopsy showed a possible slight increase in the thickness of the basement membranes of the glomerular capillaries There was an area of interstitial fibrosis incorporating a single hyalinised glomerulus, and containing groups of lymphocytes The convoluted tubules sometimes contained hyaline casts or red blood-cells Chronic pyelonephritis was diagnosed

The patient was treated with various antibiotics, none affected the course of the disease, and the proteinuria and mild hypertension persisted The child remained symptom-free until January, 1958, when she complained of severe headaches and drowsiness On admission to hospital in March, 1958, she was comatose and anuric, her blood-pressure was 260/160 mm Hg, and there was gross cardiac enlargement She died in cardiac failure shortly after admission

Necropsy

Important findings included left ventricular hypertrophy and dilatation in keeping with hypertensive heart-failure, and terminal bronchopneumonia The kidneys were three-quarters of the normal size, and each had a granular pitted surface with subcapsular petechial hæmorrhages (fig 2) Histologically the outstanding feature was severe glomerular damage In some glomeruli cellular proliferation within the capillary tuft was associated with thickening of the basement membrane, and in a few there was fibrinoid necrosis of individual capillary loops (fig 3) Many well-formed epithelial crescents were present (fig 4) More chronic changes included adhesions between the capillary tuft and the parietal layer of Bowman's capsule (fig 5), and fibrosis of the tuft There was moderate arteriolosclerosis The tubules were atrophic, and some contained hyaline casts occasionally associated with polymorphonuclear leucocytes There was much diffuse interstitial fibrosis and lymphocytic infiltration (fig 6) The appearances were those of chronic glomerulonephritis, and the capillary necroses suggested an acute terminal phase

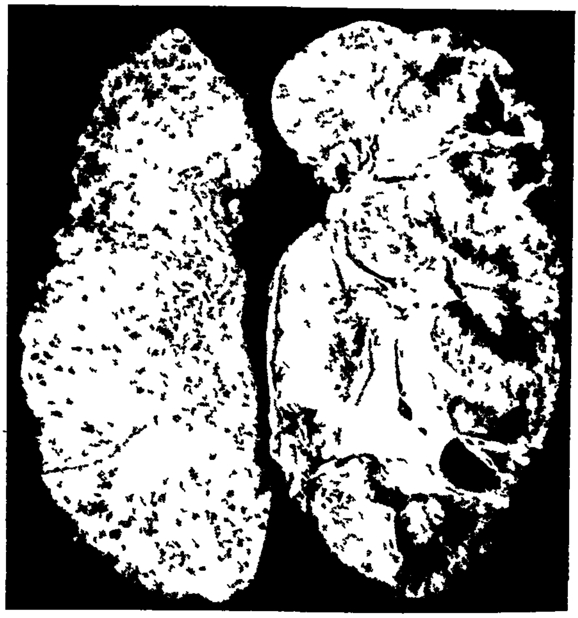


Fig 2—Case 1 kidneys $(\times {}^{2}/_{3})$

Case 2 —Bernard was admitted to hospital in July, 1953, when 7 years old, complaining of abdominal pain, vomiting, and drowsiness for two weeks Œdema and ascites were present There was slight cardiac enlargement, and the blood-pressure was 180/140 mm Hg Urinalysis revealed gross proteinuria with occasional red blood-cells and hyaline casts The hæmo-

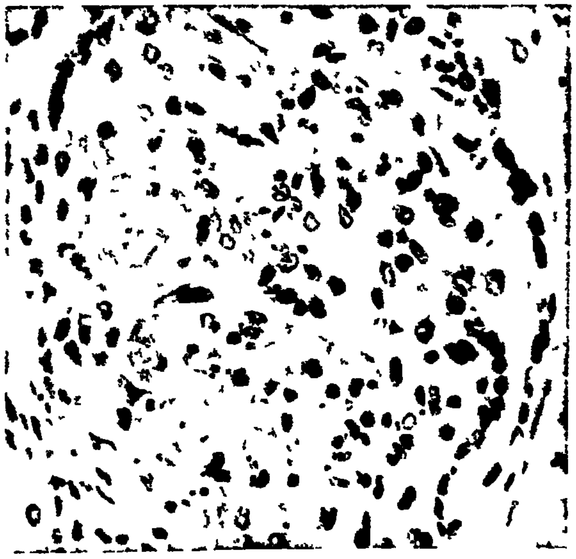


Fig 3—Case 1 glomerulus, showing fibrinoid necrosis of several capillary loops (×340)

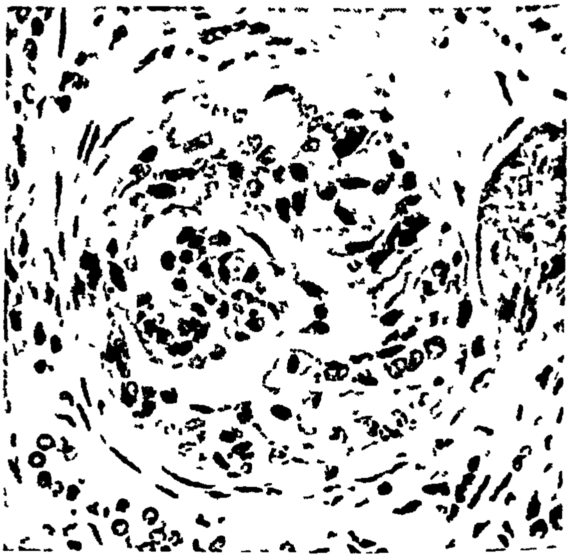
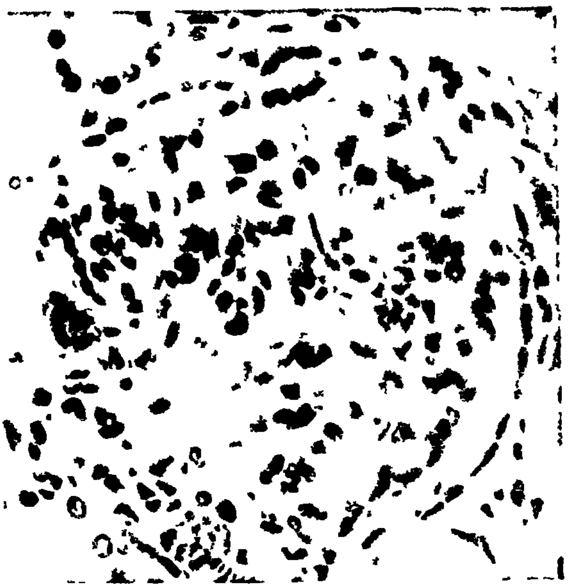


Fig 4—Case 1: glomerulus with epithelial crescent (×300)



5—Case 1 ischæmic fibrotic glomerulus with adhesions between the capillary tuft and the parietal layer of Bowman's capsule (×340)

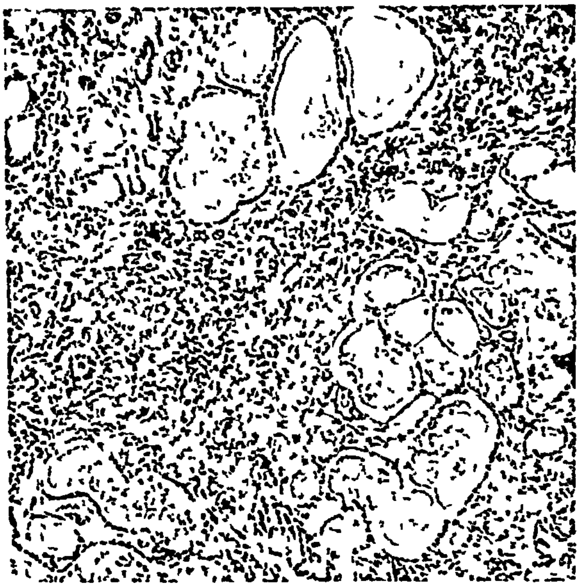


Fig 6—Case 1 low-power view showing extensive interstitial fibrosis of cortex (×110)

was 15 5 g per 100 ml , E S R 43 mm in the first hour, d-urea 112 mg per 100 ml , serum-cholesterol 476 mg 100 ml , serum-proteins 6 5 g (albumin 3 5 g , globulin g) per 100 ml The urea-clearance was 11% of the average Subacute glomerulonephritis was diagnosed Treatment with low-protein and salt-free diet was ineffec-, and renal failure progressed rapidly This was associated increasing hypertension which could not be controlled y hypotensive drugs, the patient died in cardiac failure for necropsy was refused

Case 3 —Brian was first seen in May, 1956, when he ded hospital at the age of 7 years complaining of deafness was a conduction deafness which had followed tracheo-hitis two weeks previously, and it rapidly improved uditory-nerve function was normal At this time proteinuria discovered, and on further questioning a history of fre-uency of micturition and occasional enuresis following the illness was obtained Clinical examination was His blood-pressure was 110/70 mm Hg, and was no œdema Urinalysis confirmed the proteinuria, revealed occasional red blood-cells and granular casts hæmoglobin was 15 5 g per 100 ml , E S R 14 mm in the first hour, blood-urea 48 mg per 100 ml , serum-cholesterol 330 mg per 100 ml , serum-proteins 4 25 g (albumin 2 5 g , globulin 1 7 g) per 100 ml Test of urinary specific gravity range showed a maximum specific gravity of 1020 and a minimum of 1000 Intravenous pyelography showed good concentration of the dye by both kidneys, outlining normal calyces and ureters Serum electrophoresis showed an increase in α_2-globulin, and the only abnormal finding on urinary aminoacid chromatography was the presence of the nephrosis peptide On these findings chronic nephritis was diagnosed

BIOCHEMICAL FINDINGS IN AFFECTED FAMILY

—	1956	1958		Outcome
	Urinary chromatogram	Urinary chromatogram	Serum-alkaline-phosphatase (K -A units per 100 ml.)	
Father	G.A	Normal	18	
Mother	G.A.	G.A.	16	
Allan	G.A , N	G.A	26	
Andrew	G.A., N	G.A.	18	
Barbara (case 1)	G.A., N			Died 1958
Bernard (case 2)				,, 1953
Brian (case 3)	N			,, 1957
Catherine				,, in infancy

G.A =gross aminoaciduria N =nephrosis peptide.

Treatment with cortisone for six weeks did not alter the persistent proteinuria The patient remained symptom-free till January, 1957, when he complained of severe headache At this time he had much facial œdema, and the blood-pressure was 190/160 mm Hg, but there were no other abnormal physical signs The proteinuria was gross, hæmoglobin 10 3 g per 100 ml , E S.R 58 mm in the first hour, blood-urea 89 mg per 100 ml , serum-proteins 4 35 g (albumin 2 5 g , globulin 1 85 g) per 100 ml Hypotensive drugs failed to prevent a further rapid rise in the blood-pressure, and the patient died in congestive cardiac failure

Necropsy

The finding of left ventricular hypertrophy and dilatation was in keeping with hypertensive heart-failure as the cause of death The kidneys were reduced to about two-thirds of the usual size and presented a similar appearance throughout The capsule was difficult to strip and left a granular surface with occasional subcapsular petechial hæmorrhages The cortex was much reduced in width Histologically there was considerable destruction of kidney tissue with much interstitial fibrosis and some scattered aggregations of lymphocytes All the glomeruli showed some change In many the tufts were completely or partially fibrosed, in others there were adhesions to Bowman's capsule, and a few epithelial crescents were seen The tubules were reduced in number and were atrophied Moderate arteriolosclerosis was found Chronic glomerulonephritis was diagnosed.

Other Members of the Family

Clinical examination of the 2 surviving children and the parents was normal Urinalysis and the estimates of renal function were within normal limits Abnormal findings were raised serum-alkaline-phosphatase levels, which varied from 16 King-Armstrong units in the mother to 26 King-Armstrong units in the youngest child, and the urinary aminoacid chromatograms in which there was pronounced increase in the excretion of all the aminoacids (see table) In addition, the nephrosis peptide was detected in the urine of both children

The parents are unrelated and are members of large families (fig 1) It has not been possible to examine their siblings, but all are reported to be in good health and never to have had " kidney disease ", the surviving grandparents are healthy

Discussion

In the present family 3 children died of diffuse glomerulonephritis, and the survivors, although apparently healthy, have gross generalised aminoaciduria This association, which has not to our knowledge been previously recorded, may be an ætiological factor in the present cases of glomerulonephritis

In cases 1 and 3 the diagnosis of glomerulonephritis was confirmed at necropsy The renal biopsy taken eight months before death in case 1 was in keeping with a diagnosis of *chronic pyelonephritis* A comparison of this biopsy with necropsy material suggests that the specimen was from an unrepresentative area, or that the glomerular changes were in an early phase The deafness in case 3 was related to the upper respiratory infection, and differs from that described by others in association with familial renal disease (Sohar 1956, Sturtz and Burke 1956, Perkoff et al 1958)

The pattern of the aminoaciduria is identical in all the survivors and has remained constant, except in the father, throughout the observation period of two years Aminoaciduria may occur in liver disease, but there is no conclusive evidence of this in any member of the present family It may also be due to inherited or acquired abnormalities of the renal tubules (Dent 1954), and it is presumably of renal origin in this family Lathem et al (1955) stated that glomerulonephritis does not cause any abnormality of aminoacid excretion, but aminoaciduria occurs in children with nephrosis (Squire 1953, Woolf and Giles 1956, Hooft and Herpol 1959) That the pattern of abnormal aminoacid excretion is identical in the survivors would accord better with a congenital than with an acquired condition The occurrence in two generations also suggests that it is an inherited defect, and has a genetic basis as have other syndromes associated with aminoaciduria (Harris 1957)

Earlier workers (Thomson and MacAuley 1920, Hurst 1923) referred to a *locus minoris resistentiæ* in the kidneys in familial nephritis More recently Perkoff et al (1958) suggested that renal disease in many members of a large kindred was related to "a local renal metabolic abnormality of an, as yet, unidentified nature" We believe that the aminoaciduria demonstrated in the present family may be a manifestation of such an intrinsic weakness It is recognised that some inherited defects of aminoacid excretion are associated with characteristic morphological features—e g , the "swan neck" lesion in Lignac-Fanconi disease (Darmady and Stranack 1957) We did not attempt kidney microdissection in the present series, but the presence of a renal structural defect is one way in which this organ's resistance to disease might be altered

It may be useful to divide familial nephritis into two groups (1) that associated with recognisable hereditary abnormalities (Hawkins and Smith 1950, Sturtz and Burke 1956, Goldbloom et al 1957, present series), and (2) that attributed at present solely to epidemics of the nephrotoxic streptococcus (Tudor 1943) The latter group is indistinguishable from epidemic glomerulonephritis as described by Stetson et al (1955) and many others If genetically determined defects responsible for an increased tendency to glomerulonephritis in the latter group can be identified, prophylactic chemotherapy in these families might be expected to reduce the incidence of the disease by preventing streptococcal infection

In addition to this family one other instance of familial renal disease has come to our notice In the second family 2 of 3 children have died from pyelonephritis, the diagnosis was confirmed at necropsy in 1 We did not find any abnormality of aminoacid excretion in the surviving child or in the parents

Summary

The occurrence of glomerulonephritis in 3 siblings is described The surviving members of the family all have abnormal aminoaciduria It is suggested that in this family an inherited defect responsible for the aminoaciduria also predisposes to glomerulonephritis

It is important that families with a tendency to renal disease should be recognised, and investigations of apparently unaffected members undertaken to exclude any renal defect

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PAROMOMYCIN IN THE TREATMENT OF SHIGELLA AND SALMONELLA INFECTIONS IN CHILDREN

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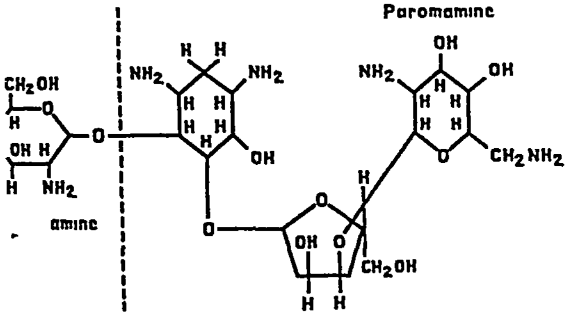
SEVERAL antibacterial drugs can control or shorten dysentery due to organisms of the shigella group Complete eradication of the infecting organism from the bowel is much more difficult In salmonella infections, persistent excretion of the infecting organism for six weeks or longer is relatively common In our hospital, irrespective of treatment, the average period required for clearance of *Salmonella typhimurium* in a recent series of children was twenty-seven days

For some time past we have been studying the effect of various drugs, singly and in combination, in cases and carriers of shigella and salmonella infections, particularly with regard to cure of the carrier state We report here the results obtained with a new antibiotic, paromomycin

Method

Paromomycin is an antibiotic derived from a strain of streptomyces Chemically, it is a glycoside of D-glucosamine, the following probable gross structure (Haskell et al)



is a white, water-soluble powder possessing bacteriostatic against various gram-negative organisms, including se of the shigella and salmonella groups For our purposes, ycin was supplied as 'Humatin' in a form suitable y for oral administration, by which route it is considered the manufacturers to be free from significant toxicity in oratory animals

The clinical trial was carried out entirely in the gastro- wards of our hospital The following patients were ed 9 children aged 1–14 years with dysentery due to gella sonnei, 18 children aged 1–16 years with symptomless by *Sh sonnei*, 8 children aged 7–16½ years in the stages of infection by *S paratyphi B*, 2 children 10 months to 8 years with symptomless infection by *typhimurium* All these infections were proved bacterio- lly by examinations of stools or fæcal swabs before

Bacteriological diagnosis was made by culturing the fæcal al on desoxycholate citrate agar with and without over- ght enrichment in selenite F or tetrathionate broth Starting y-eight hours after the last dose of drug, daily fæcal swabs r stools from each case were sent without delay to the labora- y A case was regarded as clear of infection when four negative results were obtained Specimens giving bacterial growth on culture were disregarded, in order to exclude the antibacterial effect of residual drug in the fæces During and after treatment, the specimens from each case were examined directly and by culture to detect staphylococcal or fungal superinfection

TABLE I—EFFECT OF PAROMOMYCIN ON BACTERIA IN VITRO

Organism	No of strains	Minimum inhibitory concentration (µg per ml.)	
		Bacteriostatic	Bactericidal
S typhi	1	5	20 (incomplete)
S paratyphi B	4	5–10	10–20
S typhimurium	3	10–20	20–50 (incomplete)
Sh sonnei	12	20	50 (incomplete)
Staph. aureus (Oxford)	1	5	10 (incomplete)

Sensitivity tests were performed with each strain of the infecting organisms from these patients As a routine, these were carried out by the disc-plate technique, the organism being assayed on blood-agar against blotting-paper discs impregnated with 20 µg of paromomycin base A number of assays were also carried out in broth

Treatment

All the children in the trial were nursed in bed, with barrier precautions, until clear of infection Children with severe diarrhœa were given half-strength Hartmann's solution by mouth for the first twenty-four hours, milk and water for the next twenty-four hours, and then a light diet. The paratyphoid cases were given a high calorie, low-residue diet Symptomless cases received normal diet.

Paromomycin was normally given by mouth in a syrup containing 1 g paromomycin in 4 ml (1 drachm) In a few instances it was given as a powder, in milk, or in 150 mg capsules Daily dosage, in all cases, was 40 mg paromomycin base per lb (80 mg per kg) body-weight No other antibacterial drugs were given along with paromomycin

Results

Sensitivity in Vitro

An organism was regarded as sensitive when there was a clear zone, without growth, of at least 4 mm around the margin of the disc By this criterion, all the strains of *Sh sonnei* and salmonellæ isolated from our patients were sensitive to paromomycin Tests in liquid media (table I) showed that the action of paromomycin was mainly bacteriostatic, an incomplete bactericidal effect was obtained in concentrations of 20 µg per ml against some organisms

Sonne Infection

9 children admitted with acute dysentery were treated with paromomycin, in each case the signs of infection subsided within two or three days, and 8 of the children were cured by a five-day course of treatment (table II)

18 symptomless carriers were also treated Each of these children had received other drugs, or combinations of drugs, before admission, but their stools had remained positive for *Sh sonnei* 15 were cleared of the infection after a five-day course of paromomycin, 2 were cleared after a second course, 1 child remained infected but produced negative stools after a further course of neomycin (table II)

TABLE II—TREATMENT WITH PAROMOMYCIN OF SONNE INFECTION IN CHILDREN

Type of case	No treated	Cured*	Not cured	Cured with another drug
Dysentery	9	8	1	1
Symptomless carriers	18	17	1	1
Totals	27	25	2	2

* i.e , with four consecutive negative stools

As a background to the present study, the results of treatment of cases and carriers of Sonne infection with other drugs in 1958 and 1959 were analysed (table III) As these cases were treated before we started the paromomycin trial statistical comparison would be invalid, but the results suggest that paromomycin was, to say the least, not less active than some other drugs commonly used 14 cases in this series remained positive after treatment, of these, all but 3 were clear of infection after further treatment (table III) The 2 children whose stools remained positive after paromomycin produced negative stools after neomycin was given

Salmonella Infection

10 convalescent carriers were treated with paromomycin 8 of these children had paratyphoid-B infection, 2 had *S typhimurium* infection.

The paratyphoid cases, when diagnosed, had all been treated in the febrile stage with chloramphenicol Of 12 thus treated, 8 continued to produce positive stools, and these 8 children were treated with paromomycin (table IV)

TABLE III—TREATMENT OF SONNE INFECTION IN CHILDREN WITH VARIOUS DRUGS (1958 AND 1959)

Drug	No treated	Cured*	Not cured	Cured with another drug
Streptomycin with sulphonamide†	56	46	10	8
Neomycin‡	5	4	1	1
Other drugs	6	3	3	2
Totals	67	53	14	11

* i e., with four consecutive negative stools
† Dosage 67 mg per lb body-weight daily
‡ Dosage 25 mg per lb body-weight daily

TABLE IV—TREATMENT WITH PAROMOMYCIN OF CONVALESCENT CARRIERS (CHILDREN) OF SALMONELLÆ

Infection	No treated	Cured*	Not cured	Cured with another drug
S paratyphi B	8	5	3	0
S typhimurium	2	1	1	1
Totals	10	6	4	1

* i e., with four consecutive negative stools

4 were cleared of infection after one course of paromomycin, 1 was cured by a second course 3 cases remained positive

Of the 2 children infected with *S typhimurium*, 1 gave negative stools after a single course of paromomycin

In each of the relapsing cases, the sensitivity of the reisolated organisms was retested against paromomycin No change was detected in the two strains of *Sh sonnei* or in the one strain of *S typhimurium* thus tested Of the four strains of *S paratyphi B* reisolated in relapse, two showed partial growth in the inhibitory zone around paromomycin discs on solid media On subculture, colonies from these zones were resistant to 20 µg paromomycin per ml in liquid media, whereas the parent strains were sensitive to 5–10 µg per ml This change affected only some of the bacteria in the reisolated strains, for assays of randomly selected colonies outside the inhibitory zones of the discs showed that many were still inhibited by the original levels of paromomycin

SIDE-REACTIONS

In powder form, paromomycin was distasteful but caused no upset As a syrup, it provoked mild nausea in a few older children None had nausea or vomiting

No other adverse reactions to the drug were noted In 12 children tested, hæmoglobin levels and leucocyte-counts were essentially unchanged after courses of paromomycin No abnormal changes were noted in routine samples of urine

The stools passed during the period of treatment with paromomycin were often soft and colourless, indicating some overall suppression of the fæcal flora There was, however, no evidence of serious mycotic or staphylococcal superinfection in these cases (table v) 1 child had a mild attack of diarrhœa with numerous *Candida albicans* in the fæces, a 2nd had overgrowth of candida in the stools, without symptoms

TABLE V—OCCURRENCE OF *Staph aureus* AND *Candida albicans* IN THE STOOLS OF CHILDREN TREATED WITH PAROMOMYCIN

Original infection	No examined	No of children with	
		Staph aureus	*C albicans*
Sh sonnei	27		2
S paratyphi B	8		
S typhimurium	2		

• Discussion

The infections included in this study are to a large extent self-limiting, and spontaneous clearance of the infecting organisms can occur at any time Thus any antibacterial drug must be evaluated cautiously, especially when its use is confined to acute cases The present trial included some children in whom the chronic carrier state, refractory to other forms of treatment, was well established The eradication of infection in these cases is clearly a more reliable indicator of specific activity by the drug

With these reservations, paromomycin appeared to eradicate *Sh sonnei* in a high proportion of cases and carriers In this respect it compares well with other forms of treatment in that, in our series, clearance occurred in 25 out of 27 cases in eight to twenty-four days and was as effective in chronic carriers as in acute cases

In the smaller series of children with salmonella infection, paromomycin was less effective In a larger series of salmonella infection the results obtained by McMath and Hussain (1959) were promising, especially when paromomycin was combined with streptomycin We are, therefore, inclined to support their view that paromomycin warrants a more extensive trial in this type of infection

Paromomycin proved active in vitro against various gram-negative organisms, including coliform commensals as well as pathogens This range of activity resulted in some overall suppression of the coliform fæcal flora in our patients, who passed soft, relatively odourless stools, often two or three times daily, during treatment No serious complications arose from this overall suppressive effect, nor was there during the trial any evidence of gastrointestinal irritation or systemic toxicity due to the drug

The action of paromomycin in vitro seems to be mainly bacteriostatic against *Sh sonnei* and *S typhi*, though some organisms were lysed A greater bactericidal action is exerted against some strains of *S paratyphi B* at 20 µg per ml, but this is evidently not complete enough to prevent the emergence of some resistance in vivo

No drug has been found which will consistently eliminate these species of shigella and salmonella from persistent excretors (*Lancet* 1959) In this light, the results obtained with paromomycin seem to us promising

Summary

Paromomycin, in a daily dosage of 40 mg per lb (80 mg per kg) body-weight was used in the treatment of shigella and salmonella infections

In 8 out of 9 cases, and in 17 out of 18 carriers, of Sonne infection stools were bacteriologically negative after short courses of paromomycin 5 out of 10 excretors of salmonella, similarly treated, had negative stools

No serious toxic reactions or superinfections developed Two reisolated strains of *S paratyphi B* showed partial drug resistance

Grateful acknowledgment is made to the nursing and technical staff who assisted in the work of this trial, and to Dr H W Pearson and his staff of Messrs Parke, Davis & Co, Ltd, for supplying paromomycin ('Humatin') together with helpful information about it

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"   It is through chronic illness that one understands why the family has been defined as an autocracy ruled by its sickest member   Inevitable human emotions, fear, perplexity, anger, shame, and guilt are experienced not only by the patient but by the members of his family It is important that the physician have some basic understanding of the psychology of chronic illness, of prolonged convalescence and disability so that his mind can be freed so far as possible from enslaving emotions in order that he can deal clearly and intelligently with the emotional problems of those whom he is attempting to help"—Prof JOHN ROMANO, *J chron Dis* 1955, 1, 695

ASSESSMENT OF URINARY PHOSPHATE EXCRETION

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CHANGES in parathyroid activity are known to modify the renal handling of phosphate, and this mechanism is [illegible] to account for the low serum-phosphate of hyperparathyroidism and the high serum-phosphate of hypoparathyroidism. The assessment of the degree of phosphaturia in any given patient therefore not only is of physiological interest but may be of diagnostic value (Brush et al. 1955). There is not as yet any general agreement on the best procedure for making this assessment.

The inorganic phosphate of the blood-plasma is believed to be wholly filtrable through the glomerular membrane and then partially reabsorbed by the renal tubular epithelium (Smith 1951). The phosphate appearing in the urine is generally considered to represent that proportion of the filtered phosphate which has not been reabsorbed.

It is known from phosphate infusion studies in animals (Pitts and Alexander 1944) and in man (Anderson 1955) that in acute experiments the absolute amount of phosphate reabsorbed by the tubules rises with the filtered load until at high plasma levels the tubular maximum is reached, after which further increases in plasma level and therefore in filtered load are quantitatively reflected in the urinary excretion. Hence, without a change in renal function, the renal clearance of phosphate should vary with the level of serum-phosphate. But this normal relationship between serum and urine phosphate levels will be altered by any change in the renal tubular handling of phosphate. It is such a specific change in the renal handling of phosphate which is believed to account for the abnormal levels of plasma-phosphate in parathyroid disorders.

The proportion of filtered phosphate which is not reabsorbed is represented by the ratio of the phosphate clearance to the glomerular filtration-rate, and an approximate value for the latter can be obtained from the endogenous-creatinine clearance. The resultant phosphate/creatinine clearance ratio (Cp/Ccr) has already been widely used in the assessment of parathyroid activity with varying success but in a manner which generally fails to take into account the normal fluctuations in this ratio which follow fluctuations in plasma-phosphate level (Milne et al. 1952, Nordin and Fraser 1956). The present paper re-defines the simple procedure for the measurement of this ratio which we have reported before (Nordin and Fraser 1954), describes a method of correcting the ratio to take into account the plasma level of phosphate, and reports the results obtained in various clinical conditions.

Methods

Fresh samples of urine were obtained from all the subjects together with a venous blood sample taken at about the middle of the urine collection, which was usually a two-hour period. The test is preferably performed in the fasting state, and after some days on a normal or low phosphorus intake. Catheterisation was not employed because as we have pointed out previously (Nordin and Fraser 1954) the Cp/Ccr can be calculated from the concentrations of phosphate and creatinine in the plasma and urine without considering the volume, as follows

$$\text{Cp/Ccr} = \frac{\text{Urine-phosphate} \times \text{plasma-creatinine}}{\text{Plasma-phosphate} \times \text{urine-creatinine}}$$

Inorganic phosphate and creatinine were measured in the plasma and urine by the methods of King and Wootton (1956).

Patients Studied

All the relevant cases seen in the years 1935–57 are included. The normal data were obtained from 53 members of the staff and patients convalescing from acute illnesses.

The 9 cases of primary hyperparathyroidism were all confirmed by operation.

The 17 cases of osteomalacia were inpatients with steatorrhœa, radiological thinning of the bones, and a serum calcium × phosphate product (in mg. per 100 ml.) of 25 or less. The great majority were confirmed by iliac-crest biopsy.

The 11 patients with hypoparathyroidism consisted of 9 postoperative cases, 1 idiopathic case, and 1 associated with steatorrhœa. Some of them were taking vitamin D.

The 48 cases of osteoporosis were of the type commonly called postmenopausal or senile which Nordin (1960) has defined as primary osteoporosis.

Results

Normal Subjects and Calculation of Normal Cp/Ccr

The normal relationship of plasma-phosphate to the Cp/Ccr was derived from the infusion data of previous workers as assembled and presented by Milne et al. (1952). By calculation, the regression equation of Cp/Ccr on plasma-phosphate was found to be *

$$\text{Cp/Ccr} = 0{\cdot}055 \times \text{serum-P} - 0{\cdot}07 \text{ (standard error of Cp/Ccr} = 0{\cdot}06)$$

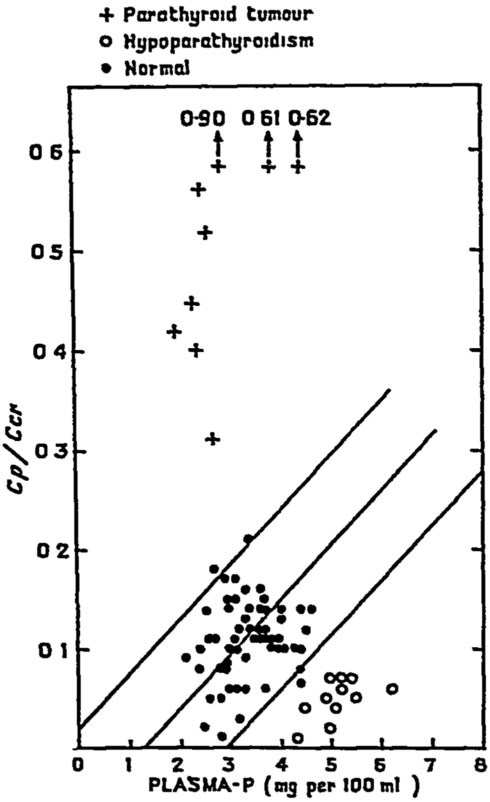

Fig. 1—Plasma-phosphate concentration and phosphate/creatinine clearance ratio in normal subjects and in patients with hyperparathyroidism and hypoparathyroidism.

The slope of the regression line is calculated from the data of Milne et al. (1952), but the limits are calculated from our normal subjects.

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* This is a more accurate recalculation of our earlier formula (Nordin and Fraser 1956) for this line Cp/Ccr = 0·05 plasma-P − 0·05 (S.E. = 0·06). The phosphate excretion index calculated by the earlier formula is almost identical with that derived from the more correct formula in this paper.

For the purpose of this calculation, and with the approval of Dr Milne, it was assumed that the data up to a plasma-phosphate of 8 mg per 100 ml fell along a straight line

The Cp/Ccr values from 53 normal subjects are shown in fig 1 in relation to this regression line previously calculated from Milne's data Their variance from this line has been calculated, and the range of 2 standard deviations was found to be ±0 09 So the estimate and variance of the normal relationship between Cp/Ccr and serum-P becomes

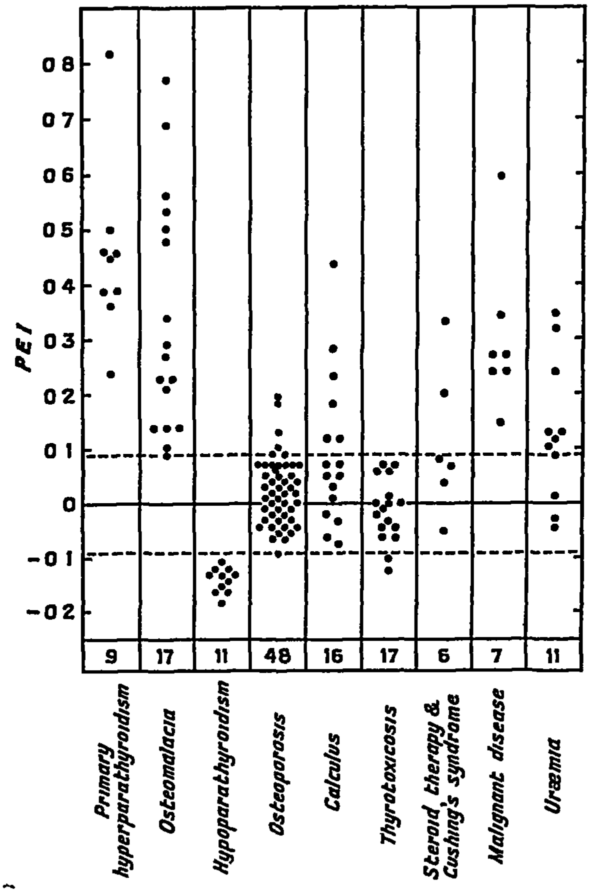
$$\mathrm{Cp/Ccr} = 0\ 055\ \text{plasma-P} - 0\ 07$$

(for normal Cp/Ccr values the range of 2 standard deviations from this estimate $= \pm 0\ 09$)

Fig 1 also shows the results obtained in 9 cases of primary hyperparathyroidism and 11 cases of hypoparathyroidism It will be seen that in the cases of hypoparathyroidism the Cp/Ccr was abnormally low in relation to the plasma-phosphate level, and that in the cases of parathryoid tumour the Cp/Ccr was above the normal range for the plasma-phosphate

Calculation of Phosphate Excretion Index (P E I)

By applying the above regression-line equation to the plasma-phosphate level in any given case, it is possible to predict what the mean Cp/Ccr should be in normal circumstances, and so to measure the extent to which the observed Cp/Ccr differs from the predicted one A difference of less than ±0 09 denotes a point falling within our normal limits, larger differences represent points falling outside these lines It is therefore possible to represent the extent to which any given observation departs from the predicted mean by a single value which we have called the phosphate excretion index (P E I), and the results obtained in various metabolic disorders are shown in this way (fig 2) As well as the 9 cases of parathyroid tumour, 16 out of 17 cases of osteomalacia had P E I values of more than +0 09 In addition, high values were observed in 4 out of 48 cases of osteoporosis (2 of them diabetics), 6 out of 16 cases of renal stone, 3 out of 6 patients with Cushing's syndrome or on steroids, 7 out of 7 cases of malignant disease with bone secondaries, and 7 out of 11 cases of uræmia Low values are found in all 11 cases of hypoparathyroidism and 2 out of 17 cases of thyrotoxicosis



2—Phosphate excretion index in various clinical disorders

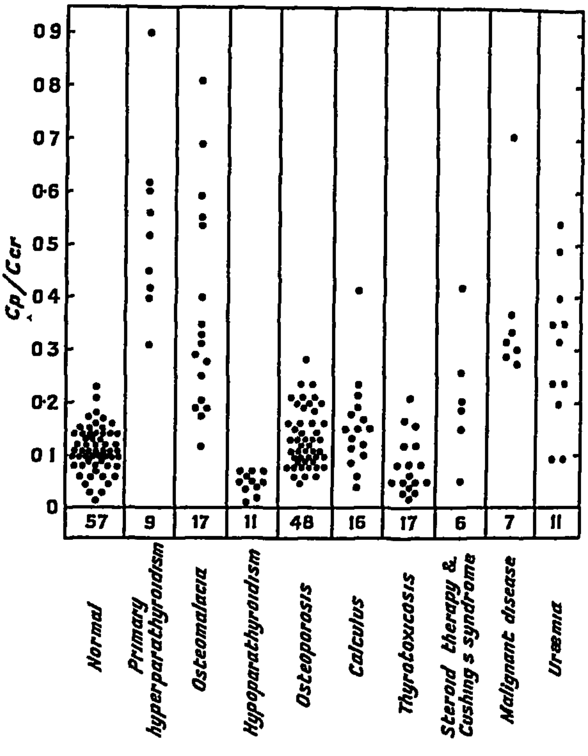


Fig 3—The phosphate/creatinine clearance ratio in the normal subjects and in the cases shown in fig 2

Alternative Indices of Phosphaturia

Simple Cp/Ccr—Fig 3 shows the actual values of Cp/Ccr in the same cases without the application of any correction for plasma-phosphate level It demonstrates that the "normal" range of Cp/Ccr extends from about 0 02 to 0 22, and that it is quite impossible to separate the different diagnostic categories from one another on this calculation alone In particular, it is impossible to separate cases of hypoparathyroidism and osteomalacia from the normal subjects

Urinary phosphate/creatinine ratio (P/Cr)—Milne (1951) has shown that there is a correlation between plasma-phosphate and urine-phosphate output in mg per hour in normal subjects, but we have found that inaccuracies in bladder emptying make this relationship of little diagnostic value unless the samples are obtained by catheter In normal subjects, however, an equivalent relationship exists between the plasma-phosphate level and the ratio of phosphate to creatinine in the urine, and fig 4 shows the data on the same cases plotted in this way The regression of the urinary phosphate/creatinine ratio (P/Cr) on the serum-phosphate has been calculated as follows

$$\mathrm{P/Cr} = 0\ 145 \times \text{serum-phosphate} - 0\ 12$$

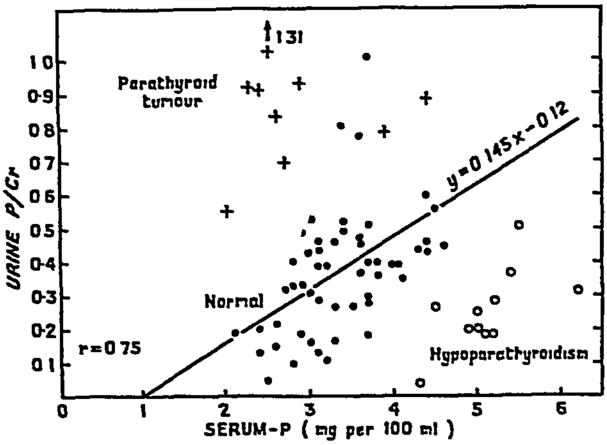


Fig 4—Relationship between plasma concentration of phosphate and ratio of phosphate to creatinine in urine in normal subjects and in hyperparathyroidism and hypoparathyroidism

The coefficient of correlation is 0 75 All 11 cases of hypoparathyroidism fall below and to the right of the normal data, and 7 out of 9 cases of parathyroid tumour above and to the left the other 2 were uræmic.

P E I with assumed plasma-creatinine of 1 mg per 100 ml—The existence of a relationship between urinary P/Cr and plasma-phosphate suggests that the estimation of plasma-creatinine might not be essential to the calculation of Cp/Ccr, and that in the absence of renal failure an arbitrary figure could be substituted for what is at best an unsatisfactory estimation. Fig 5 therefore shows the P E.I on all the cases represented in figs 2–4 (except those with uræmia) calculated with an assumed plasma-creatinine of 1 0 mg per 100 ml Comparison with fig 2 shows that the separation of the cases of hyperparathyroidism from the normal range is less satisfactory by this calculation and that more cases of osteoporosis appear to have hyperphosphaturia

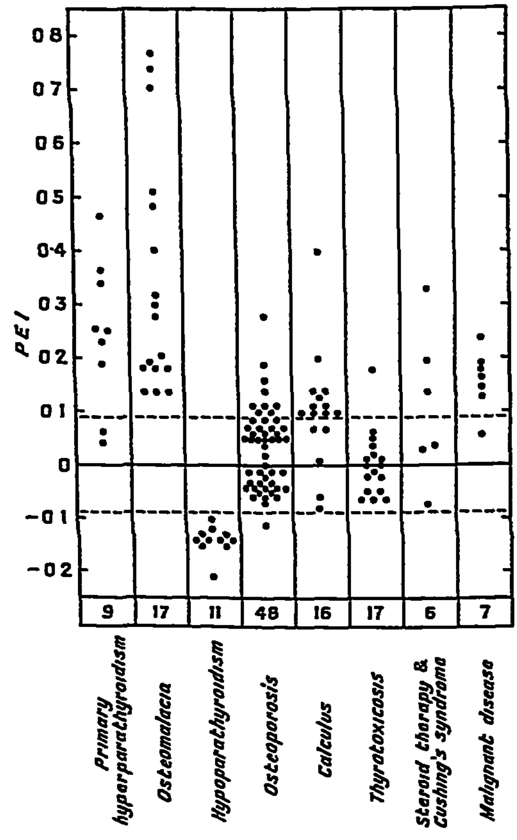


Fig 5—Phosphate excretion index calculated with an assumed plasma-creatinine concentration of 1 0 mg per 100 ml.

"*Reabsorbed-phosphate*" *index*—Yet another method of assessing urine phosphate excretion has been suggested by Thomas et al (1958) and by Morgan (1959) If the inferred tubular reabsorption of phosphate (1-Cp/Ccr) is multiplied by the plasma-phosphate a figure is obtained which represents approximately the amount of P reabsorbed per 100 mg glomerular filtrate If this calculation is applied to our data the results shown in fig 6 are obtained The absolute normal range is 1 8–4 0 mg P reabsorbed per 100 ml of filtrate The separation of the cases of osteomalacia from the normal subjects is less satisfactory than by the P E I procedure (fig 2) but the most striking difference is that most cases of uræmia yield results in the normal range.

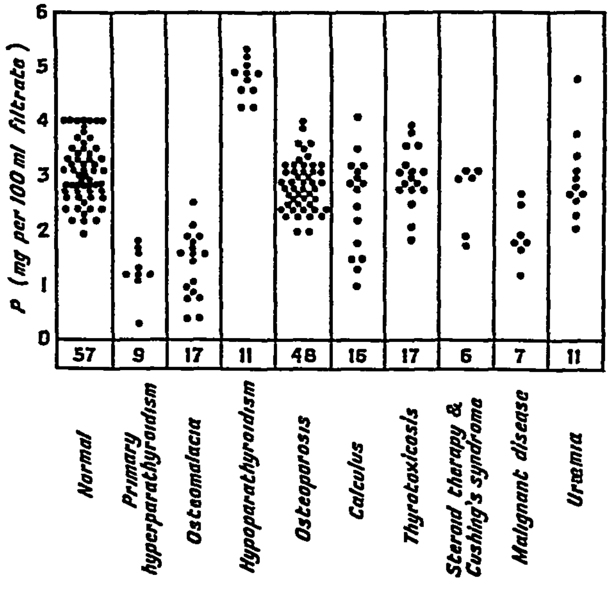


Fig 6—Mg of phosphate reabsorbed per 100 ml of glomerular filtrate in various clinical disorders

Routine Use of the P E I

The results obtained in 350 consecutive observations of P E I on 103 patients are shown in the accompanying table 164 of these observations (on 55 patients) fell within the normal range 186 on 48 patients were either high or low The most striking feature of these observations is the high values found in patients taking large supplements of calcium glycerophosphate

Discussion

We have shown that when the plasma P and the Cp/Ccr are considered in relation to one another, cases of primary hyperparathyroidism have a high clearance ratio and cases of hypoparathyroidism a low clearance ratio in relation to the concentration of plasma-phosphate. High clearances with low values for plasma-phosphate are also found in osteomalacia, presumably owing to the secondary hyperparathyroidism which is known to occur in this condition This accords with our earlier data (Nordin and Fraser 1956) which have recently been confirmed by Talpers and Stein (1959)

ANALYSIS OF 350 CONSECUTIVE P E I OBSERVATIONS

—	Total no of observations	Total no of cases	High values	Low values
Hypoparathyroidism on various doses of calciferol	122	4	30	46
Osteomalacia	61	5	57	0
Steatorrhœa (without osteomalacia)	13	3	1	2
Osteoporosis	34	34	4	0
„ on P supplements	85	36	39	0
Parathyroid tumour	2	2	2	0
Patients on steroids	10	1	1	0
Uræmia	5	1	1	0
Renal calculus	6	6	2	0
Thyrotoxicosis	3	3	0	0
Cushing's syndrome	1	1	1	0
Normal	8	7	0	0

For convenience in making this comparison in relation to plasma-phosphate, we have suggested the calculation of the phosphate excretion index which measures departures from the normal relationship and separates hyperparathyroid, euparathyroid, and hypoparathyroid cases from each other We have not yet come across any false negatives (i e, normal values in primary hyperparathyroidism) with this procedure, but we are aware that they occasionally occur (McGeown 1957, G H Morgan, personal communication) As far as false positives are concerned, it is clear that high values are usually seen in osteomalacia and *frequently in uræmia*, but this we attribute to the secondary hyperparathyroidism which is known to occur in these conditions (Nordin 1958) We have also seen high values in some cases of renal calculus without raised plasma-calcium but with hypercalciuria these are examples of the syndrome of idiopathic hypercalciuria (Henneman et al 1958) and may in fact represent a form of hyperparathyroidism or tubular disease, but we have also seen many normal values with hypercalciuria High values are also seen in some cases of malignant disease with hypercalcæmia in which other workers have already reported a low rate of tubular reabsorption of phosphate (Thomas et al 1958) these latter cases are therefore biochemically indistinguishable from primary hyperparathyroidism Abnormally high values for P E I may also be found in patients with Cushing's syndrome or on steroid therapy, in accordance with other evidence that the steroids reduce the renal tubular reabsorption of phosphate (Anderson 1959) Possibly this could be secondary to the rise in the filtered load of glucose which may occur in states of adrenocortical overactivity, since there is considerable evidence that phosphate and glucose compete for the same tubular reabsorptive pathway (Huffman et al 1958) This may also explain the high values seen for P E I in 2 cases of osteoporosis with diabetes mellitus, the high values in 2 other cases of osteoporosis out of 48 measured are unexplained Clearly, however, the parathyroid hormone is only one of several factors which may influence the excretion of phosphate—albeit one of the major factors

Our data suggest that the measurement of the P E I provides some information about the excretion of phosphate in any given case and indicates whether or not it can be regarded as normal, although we are aware that the Cp/Ccr on which it is based does not measure accurately the proportion of filtered phosphate that is reabsorbed Our data also suggest that this index of phosphaturia is better than the available alternative indices

Various other ways have been suggested of assessing the rate of phosphate excretion Many workers assume that the creatinine clearance is identical with the glomerular filtration-rate and subtract the Cp/Ccr from 1 to yield the tubular reabsorption of phosphate (T R P) which they express as a percentage (Chambers et al 1956) We agree with Hills and Burr (1958) that there is no advantage in this procedure and that it introduces an assumption which is unjustified Other workers (Kyle et al 1958) have confined themselves to the measurement of an absolute phosphate clearance calculated from a timed sample of urine The preliminary results with this procedure are good so far as they go, but we believe from experience that sufficient accuracy to make this a useful procedure can only be obtained by catheterisation and we consider this unjustified in this context

Both these procedures suffer furthermore from the weakness that they do not take into account the prevailing level of phosphate in the plasma As we have shown in fig 3, relatively poor separation between the various degrees of parathyroid activity is achieved by measuring the Cp/Ccr alone, and the same must be true of the T R P and the simple phosphate clearance

Certain workers (Thomas et al 1958) have suggested an alternative method of correction for the plasma-phosphate concentration They multiply the plasma-phosphate concentration by the T R P and express the results as mg of P reabsorbed per 100 ml of glomerular filtrate As we have shown in fig 6, this calculation separates the various groups in much the same way as our calculation except that a few cases of osteomalacia and more cases of uræmia fall into the "normal" range In fact, normal or even "hypoparathyroid" values are obtained in most cases of uræmia with high levels of plasma-phosphate, whereas in such cases the P E I is almost invariably raised In view of the abundant evidence of secondary hyperparathyroidism in glomerular renal failure (Goldman and Bassett 1954, Nordin 1958) we believe that the P E I calculation is probably sounder than the calculation of mg P reabsorbed per 100 ml of glomerular filtrate, although we agree that the latter is a simple and attractive procedure

It must be emphasised that our normal standards are not applicable to subjects on very high intakes of phosphorus The disproportionate rise in phosphate clearance in these circumstances has already been reported by Crawford et al (1950) and Goldman and Bassett (1958) and is being studied by us at present It is well seen in our cases of osteoporosis taking calcium-glycerophosphate supplements and may be due to stimulation of the parathyroid glands by a raised serum-phosphate concentration

Summary

The normal relationship between the plasma-phosphate concentration and the phosphate/creatinine clearance ratio has been calculated from the phosphate infusion data of other workers

A simple procedure is described for determining the phosphate/creatinine clearance ratio and for calculating the extent to which it departs from the predicted normal value in any particular case We have called this deviation from the normal value the phosphate excretion index The normal range of this index is −0 09 to +0 09

The clearance ratios were found to be abnormally high in relation to the plasma concentration of phosphate in primary hyperparathyroidism and in osteomalacia but abnormally low in hypoparathyroidism

Abnormally high values were found in certain other conditions, some of which may be biochemically indistinguishable from hyperparathyroidism

References at foot of next column

PLASMA-INSULIN ACTIVITY IN ACROMEGALY AND SPONTANEOUS HYPOGLYCÆMIA

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IN recent years various methods for assaying plasma-insulin activity have been used in the study of cases of spontaneous hypoglycæmia, acromegaly, diabetes, and other conditions in which abnormal levels might be expected The results of these assays appear to have led clinicians to believe that in some conditions a knowledge of the level of plasma-insulin activity is of significance for diagnostic or therapeutic purposes To assess the value of such assays from this point of view, I have used the rat-diaphragm method in cases of acromegaly and spontaneous hypoglycæmia In both these conditions abnormal levels have been reported

Materials and Methods

Plasma Specimens

Heparinised blood was drawn with the subject at rest after an overnight fast Following the separation of the plasma within one hour of collection, its glucose content was determined and raised to approximately 300 mg per 100 ml by the addition of solid glucose Such plasma was stored at −10°C and diluted, where necessary, by the addition of glucose-saline buffer (see below) immediately before assay

Estimation of Plasma-insulin Activity

A standardised assay procedure was used throughout these experiments (Wright 1957) The mean *glucose-consumption rate* of a group (three to eight) of hemi-diaphragms from eight rats incubated individually in undiluted plasma (2 ml) was compared with that of another incubated in Krebs-Ringer bicarbonate buffer (2 ml.) containing glucose in a concentration of approximately 300 mg per 100 ml (glucose-saline buffer) The difference between the mean glucose-consumption rates of these two groups of hemi-diaphragms is termed the *insulin effect* of the plasma Usually the hemi-diaphragms incubated in these two media did not come from the same rats, they were not paired In no case were both hemi-diaphragms from any one rat incubated in the same medium In most experiments other hemi-diaphragms were incubated in glucose-saline buffer containing insulin in concentrations of 10, 100, and 1000 micro-units per ml , when diluted plasma of normal and acromegalic subjects was studied the effects of insulin were not examined

The glucose-consumption rates and insulin effects are expressed as µg glucose per 10 mg dry weight of tissue per 90 min , hemi-diaphragms were weighed in the dry state and incubated for 90 min

The mean *insulin equivalent* of any group of plasma specimens was deduced from its mean insulin effect and the mean effects produced by the three standard concentrations of insulin in these experiments (table I), it has been shown (Vallance-Owen et al 1954, Wright 1957) that there is a direct relationship between glucose-consumption rate and the cube-root of the insulin concentration in the incubation medium The insulin equivalent deduced from the mean effects produced by groups of diluted plasma specimens is stated in terms of undiluted plasma, the necessary corrections having been made for the degree of dilution used

Results

EFFECT OF INSULIN ON GLUCOSE UPTAKE

The insulin effects produced by the pure hormone in the three concentrations used in varying combinations in 54 experiments are shown in table I, they are not significantly different from the results previously reported (Wright 1957)

TABLE I—STIMULANT EFFECTS OF INSULIN ON GLUCOSE CONSUMPTION BY THE ISOLATED RAT-DIAPHRAGM

Insulin concentration (micro-units per ml)	Experiments (no)	Mean insulin effect * (µg glucose per 10 mg dry wt per 90 min) ± S E.M
10	19	39 ± 12
100	26	145 ± 8·0
1000	54	237 ± 6 3

* Insulin effect in individual experiments = mean glucose uptake of hemi-diaphragms incubated in presence of insulin minus mean uptake of those incubated in its absence

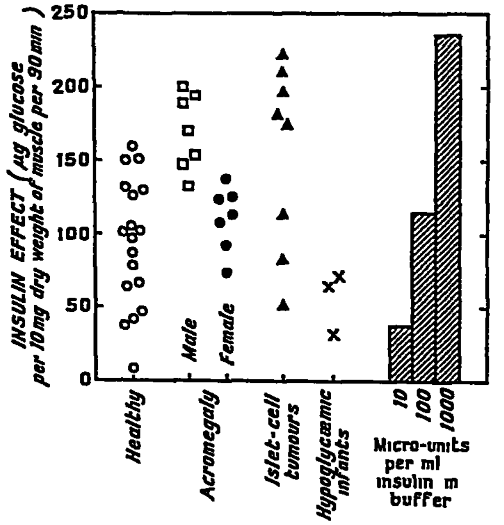
HUMAN PLASMA

The insulin effects of undiluted plasma samples from 43 persons are shown graphically in the accompanying figure

Normal Subjects

The mean insulin effect of undiluted plasma from 18 fasted normal subjects (14 males and 4 females) was 94 (S D = 44) It is therefore unlikely (P = 0 95) that an individual specimen from a normal person would produce an effect greater than 182

In 9 of these cases, all male, diluted plasma was assayed In each experiment eight rats were used, four



Insulin effects of undiluted plasma from fasting subjects and of standard insulin solutions in buffer

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TABLE II—INSULIN EFFECTS OF UNDILUTED AND DILUTED PLASMA FROM FASTED NORMAL AND ACROMEGALIC SUBJECTS

Subjects	No	Sex	Mean insulin effect *			Mean insulin equivalent †		
			P	P/4	P/16	P	P/4	P/16
Normal	9	M	100 (*7*)	90 (*11*)	34 (*8*)‡	74	200	
Acromegalic	7	M	170 (*10*)	150 (*9*)	110 (*13*)	360	1000	1500
	7	F	111 (*8*)	104 (*13*)	60 (*9*)	104	360	310

* µg glucose per 10 mg dry wt. muscle per 90 min , for undiluted plasma (P) and plasma diluted 1 4 (P/4) and 1 16 (P/16) in glucose-saline buffer S E.M shown in parentheses
† micro-units per ml
‡ Only 4 specimens examined

hemi-diaphragms from different animals being incubated individually in each plasma medium In all 9 cases undiluted plasma and plasma diluted 4-fold in glucose-saline buffer were used as incubation media, but in only 4 was 16-fold diluted plasma employed Table II shows that the mean *insulin effect* of plasma diluted 4-fold is not significantly different from that of undiluted plasma, whereas that of plasma diluted 16-fold is much smaller

The mean *insulin equivalent* of the undiluted plasma is 74 micro-units per ml Plasma assayed after 4-fold dilution has a mean insulin equivalent of 200 micro-units per ml Little significance can be attached to the insulin equivalent deduced from the mean insulin effect produced by plasma diluted 16-fold, which was only weakly active It seems unlikely, however, that the insulin equivalent is increased further when the degree of plasma dilution exceeds 1 4

Acromegalics

Plasma samples were examined from 7 male and 7 female patients with typical clinical signs of acromegaly All were normoglycæmic in the fasting state

Abnormal plasma-insulin activity appears to be confined to the male patients Thus, table II shows that the mean effect produced by undiluted plasma from male acromegalics is significantly greater ($P < 0\ 01$) than that of plasma from the females, which is not significantly different from that of the 9 normal males No significant change in mean plasma-insulin effect was noted in either the male or the female acromegalics on 4-fold dilution of the plasma, though in both cases further dilution did result in a fall in mean insulin effect The main difference between these two groups is that the mean insulin effect produced by plasma of male acromegalics is greater than that of females at all degrees of dilution

The mean insulin equivalent of undiluted plasma from the male acromegalics (360 micro-units per ml) is approximately 5 times that of plasma from normal subjects Similarly the mean equivalents of plasma assayed after 4-fold (1000 micro-units per ml) and 16-fold (1500 micro-units per ml) dilution are at least 5 times the values observed in similarly diluted normal plasma In female acromegalics the plasma insulin equivalents at all degrees of plasma dilution are not significantly different from those of normal plasma

TABLE III—INSULIN EFFECTS OF UNDILUTED PLASMA FROM FASTED SUBJECTS WITH SUBSEQUENTLY PROVEN ISLET-CELL TUMOURS OF PANCREAS

Case no	Age (yr)	Sex	Duration of symptoms (yr)	Plasma-sugar (mg per 100 ml)	Insulin effect (µg glucose per 10 mg dry wt. per 90 min)	Insulin equivalent (micro-units per ml)
1	45	F	10	33	84 (±*7*)	52
2	32	M	1	65	114 (±*15*)	118
3	43	M	1	28	119 (±*22*)	590
4	54	F	¹/₂	47	176 (±*15*)	420
5	52	M	1	39	223 (±*49*)	830
6	54	F	¹/₂	24	53 (±*23*)	14
7	31	M	2¹/₂	25	212 (±*8*)	730

S.E.M. shown in parentheses

Islet-cell Tumours of the Pancreas

Plasma was examined in 7 cases from whom histologically proven islet-cell tumour tissue was subsequently removed Blood was drawn after at least a 12-hr fast, and in 6 cases the patient was hypoglycæmic at the time Paired hemi-diaphragms from five rats were incubated in (*a*) undiluted plasma and (*b*) glucose-saline buffer, the mean insulin effects produced in each case are shown in table III High insulin effects were observed in only three cases (nos 3, 5, and 7), the remainder being within the normal range (see figure)

Idiopathic Hypoglycæmia of Infancy

Plasma was obtained from 3 young children who had had repeated spontaneous attacks of hypoglycæmia for which no cause could be found At the time of blood collection all were hypoglycæmic (plasma-glucose concentration <40 mg per 100 ml) and in 2 cases symptoms appeared soon afterwards The insulin effects produced by these plasma specimens were essentially normal (see figure)

Discussion

Normal Subjects

The present results confirm previous observations that undiluted plasma from fasted normal subjects has a mean insulin effect equivalent to that of the pure hormone in a concentration of 50–100 micro-units per ml (Vallance-Owen and Hurlock 1954, Wright 1957) This value is somewhat less than the range (50–350 micro-units per ml) obtained more recently by Martin et al (1958) who used the epididymal-fat-pad method of insulin assay

Randle (1957a), using the isolated rat diaphragm, found that the insulin content of plasma assayed after 4-fold dilution was greater than that assayed in the undiluted form, in other words, plasma diluted 4-fold contains more insulin than one would expect following this degree of plasma dilution Further dilution, however, decreased the insulin content in proportion to the degree of dilution used (Randle 1954c, 1957a) This paradoxical situation was also observed by Takeuchi et al (1957), who used dog plasma, and is confirmed by the present results

The insulin equivalent of plasma assayed after 4-fold dilution is of the order of 200 micro-units per ml , judging by the present results, higher levels are unlikely to be obtained if plasma is assayed in a more dilute form Of those who have used diluted plasma or serum for assay in vitro Groen et al (1952) and Takeuchi et al (1957) have obtained results of this order On the other hand, Randle (1954c, 1957a), Willebrands and Groen (1956), and Willebrands et al (1958), who also used diluted plasma, suggest that normal plasma contains insulin in concentrations greater than 1 milli-unit per ml These very high levels have not yet been adequately explained, and it seems unlikely that the effect produced by plasma dilution is entirely responsible

Acromegalics

The plasma of acromegalic patients was examined with two objects in view First it was thought that some relationship might exist between the plasma-insulin effect and the degree of functional activity of the pituitary tumour Secondly, some confirmation of the very high levels of plasma-insulin activity reported by Randle

(1954a, 1955, 1957b) in acromegalic patients seemed desirable.

The injection of growth hormone into normal cats increases plasma-insulin activity (Randle and Young 1956), and the removal or irradiation of the pituitary tumours of acromegalic patients reduces their previously high levels of plasma-insulin activity (Randle 1954a, 1955). From these observations and the low level of activity found by Randle (1954b) in plasma from patients with hypopituitarism, it was inferred that high levels of plasma-insulin activity might be found only in those cases in which the pituitary tumour was in an active secretory state. On the basis of clinical observations and the results of various laboratory investigations (J. H. Briggs, W. J. H. Butterfield, P. H. Wright, unpublished) the 14 acromegalics (table II) were classified according to the degree of tumour activity thought to be present. Contrary to expectations, however, very active plasma was obtained from clinically inactive cases, and patients with active tumours yielded only weakly active plasma. It was, however, noted that male acromegalic patients, whose plasma-insulin activities were generally higher than those of the females, were also more resistant to the effects of intra-arterial insulin (Hardwick et al. 1959).

In no case were the plasma-insulin equivalents comparable with the high values (40–500 milli-units per ml.) reported by Randle (1954a, 1955) even when diluted plasma was used for assay. It seems probable, therefore, that, as in the case of normal plasma, some factor other than plasma dilution is responsible for the extremely high figures reported by Randle.

Islet-cell Tumours of the Pancreas

Although several groups of workers (Groen et al. 1952, Vallance-Owen et al. 1955, Kelly 1956, Willebrands and Groen 1956, Randle 1957a) have reported high levels of activity in plasma or serum obtained from such cases, this finding is not invariable. Willebrands and Groen (1956), who studied 11 proven cases, found abnormally high levels of activity in only 7. The present findings confirm that a normal level of activity may be found in subsequently proven cases of insulin-secreting tumours of the pancreas. Failure to demonstrate abnormal insulin activity in the plasma may be due to incorrect timing of the blood sample. Willebrands and Groen (1956), for example, have reported 2 cases in which samples were drawn on more than one occasion, and in both cases normal and high levels were recorded at different times. The finding of a single normal plasma-insulin level in no way contraindicates the diagnosis.

Idiopathic Hypoglycæmia of Infancy

Though a rare condition, spontaneous hypoglycæmia of infancy can cause permanent mental impairment if it is not recognised and adequately treated (McQuarrie 1954). In a large proportion of cases the underlying cause is not known, and the part played by endogenous insulin secretion has not been assessed. For this reason treatment in most cases has been empirical and has been directed towards abolishing the hypoglycæmic attacks responsible for the cerebral damage. Attempts have however been made in recent years to identify those cases which are due to increased insulin secretion by the pancreas or by an islet-cell tumour, and which would therefore benefit by surgical treatment.

Randle examined plasma from 3 of the cases described in detail by Cochrane et al. (1956), but in only 1 did he find high plasma-insulin activity. Laparotomy in this case revealed an abnormally large amount of islet-cell tissue made up predominantly of β-cells; partial pancreatectomy produced temporary relief. Both of the other cases had normal plasma-insulin levels though 1, which was submitted to laparotomy, showed hyperplastic changes in the pancreatic islet tissue. Vallance-Owen also examined plasma from a case described by Kinsbourne and Woolf (1959) and reported a normal level of activity; no laparotomy was performed. Of the cases examined here only 1 was submitted to laparotomy, and again hyperplastic changes were reported in the islet tissue. In all 3 cases, however, normal levels of plasma-insulin activity were found (see figure). It appears, therefore, that even in those cases where there is collateral evidence of increased β-cell activity in the pancreas, normal plasma-insulin levels may be found.

COMMENT

The results of the present experiments and a review of other published work show that for diagnostic and therapeutic purposes plasma-insulin assays are of little practical use in individual cases. On the other hand, in studies of groups of patients with the same clinical conditions they have provided useful information.

A small proportion of the patients who present with clinical signs of spontaneous hypoglycæmia are ultimately shown to have islet-cell tumours of the pancreas (Conn and Seltzer 1955). These cases can usually be identified by rigorously applying simple clinicopathological tests, such as those suggested by Whipple (1952). Knowledge of the plasma-insulin activity in suspected cases apparently provides no more reliable information than the results of these much simpler investigations. The results may, in fact, be misleading unless it is appreciated that a normal level of plasma-insulin activity does not contraindicate the diagnosis. In other conditions, such as acromegaly, diabetes, spontaneous hypoglycæmia of infancy, hypopituitarism, and possibly others in which carbohydrate metabolism is deranged, the results of other and simpler investigations are of more significance to the clinician in individual cases than a knowledge of the plasma-insulin level.

On the other hand, the hypotheses put forward by Himsworth and Kerr (1939) and later by Lawrence (1951) to explain the existence of two contrasting clinical types of human diabetes were confirmed when their plasma-insulin levels were investigated; no insulin-like activity is detectable in the plasma of young ketotic diabetics who require insulin therapy for survival, while essentially normal levels are found in the plasma of the older obese group (Bornstein and Lawrence 1951, Vallance-Owen et al. 1955). Similar useful information has been obtained from studies of acromegalics and of animals treated with growth hormone.

The abnormal levels of plasma-insulin activity reported in acromegalic patients and in normal cats treated with growth hormone appear to be due to increased insulin secretion by the pancreas (Randle and Young 1956, Randle 1957b). If, as previously suggested (Wright 1957), the effect produced by undiluted plasma is due to the biologically effective circulating insulin and that of diluted plasma is a measure of the total insulin content, then the plasma of male acromegalics contains 5 times (360 micro-units per ml.) the concentration of biologically effective insulin and at least 5 times (1·0–1·5 milli-units per ml.) the total amount of insulin present in normal plasma, as in normal plasma, about two-thirds circulating hormone is inactive The substance which inactivates the circulating insulin in acromegalic patients may be similar to, if not identical with, the insulin inhibitor extracted from normal plasma by Vallance-Owen et al (1958a and b), this substance is not present in the plasma of hypophysectomised patients, and its inhibitory action is disproportionately reduced by dilution Thus the abnormal insulin effects produced by diluted plasma from male acromegalics could be due to the presence in undiluted plasma of large amounts of an insulin inhibitor whose effects are abolished by plasma dilution, no such inhibitor has yet been isolated or identified The abnormal amount of insulin present in undiluted plasma may be necessary to compensate for the abnormal resistance of otherwise sensitive peripheral tissues This hypothesis, though it may account for the high levels of activity observed in male subjects, does not explain why undiluted and diluted plasma from comparable female acromegalics have essentially normal levels of activity

Randle (1956) has shown that the rat-diaphragm method of insulin assay is " sensitive but not very precise " —an assessment with which Willebrands and Groen (1956) agree Concentrations of the order of 100 micro-units per ml were easily detected in the present experiments, though in lower concentrations (10 micro-units per ml) insulin did not always produce significant effects in individual experiments The insulin equivalent values deduced from the effects produced by individual plasma specimens must be regarded as only approximate the correct value may be anything from a half to twice the estimated figure Thus, though this method of assay is very sensitive, its inaccuracy may be responsible for its failure to provide information of clinical significance in individual cases There is considerable evidence (Groen et al 1952, Randle 1954c, Vallance-Owen and Hurlock 1954, Randle and Taylor 1958) that the biological effects produced by plasma are due to the insulin which it contains, but other substances may also be present which augment or diminish its effects Further investigations, similar to those of Field and Stetten (1956) and Vallance-Owen et al (1958a and b) and aimed at the detection and identification of such inhibitors and augmentors in plasma, may yield more useful information concerning abnormal carbohydrate metabolism in human disease than the less specific plasma-insulin assays carried out in the past

Summary

Insulin assays were carried out on plasma drawn from 18 normal subjects, 14 acromegalics, 7 patients with islet-cell tumours of the pancreas, and 3 children with idiopathic spontaneous hypoglycæmia

Normal undiluted plasma has a biological effect equivalent to that of insulin in a concentration of approximately 70 micro-units per ml The insulin equivalence of plasma diluted at least 4-fold is about 200 micro-units per ml

Plasma from female acromegalics, assayed in the undiluted and diluted form, has essentially normal biological activity, while at all levels of dilution plasma from male acromegalics is significantly more active It is suggested that the latter contains high concentrations of an insulin inhibitor

Plasma from 3 of the cases of islet-cell tumours was abnormally active It is concluded that normal levels of activity in suspected cases do not contraindicate this diagnosis

Normal levels of activity were found in the 3 cases of spontaneous hypoglycæmia of infancy

Whereas knowledge of plasma-insulin activity may help to explain the underlying causes of abnormal carbohydrate metabolism in some pathological conditions, assays in individual cases seldom provide information of use to the clinician

I should like to thank those clinicians of other hospitals who kindly supplied me with plasma from the cases of spontaneous hypoglycæmia, Dr P M Bishop, Prof W J H Butterfield, and Dr J H Briggs for their cooperation in the study of acromegalic patients carried out in this hospital, Prof R. H S Thompson for his encouragement and advice, and Mr K G Kilbourn for his skilled technical assistance

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LEUCINE AND PELLAGRA

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PELLAGRA has long been known to be predominantly a disease of maize-eaters The association of pellagra with maize consumption has been attributed, among other factors, to the low tryptophan content of maize, and to the poor availability of its nicotinic acid The disease is rare in areas where rice constitutes the staple In nearly ten years' experience with many cases of nutritional deficiencies, we have seen only 4 classical cases of pellagra among the rice-eating population of Coonoor

On the other hand, in Hyderabad, a city nearly five hundred miles further north, we frequently encounter cases of pellagra Careful examinations of the dietaries of the poor segments of the population in Coonoor and Hyderabad failed to reveal any striking differences with regard to the intake of different nutrients, but, whereas rice is the sole staple in Coonoor, the dietaries of the poor segments of the population in Hyderabad invariably include the millet *Sorghum vulgare* (jowar) In practically every case of pellagra investigated by us in Hyderabad, a history of regular consumption of jowar with or without

AMINOACID COMPOSITION OF MAIZE, JOWAR, AND RICE

—	Tryptophan‡	Leucine‡	Isoleucine‡	Nicotinic acid§
Maize*	0·8	14·9	6·4	1·4
Jowar†	1·2	12·9	6·1	1·8
Rice†	1·2	8·0	6·0	1·2

* Baumgarten et al (1946) ‡ g per 100 g protein
† Balasubramanian et al (1952) § mg per 100 ml

rice was obtained. In only 1 case was there a history of consumption of maize in addition to jowar and rice.

Comparison of the chemical composition of rice, jowar, and maize (see accompanying table) shows that the nicotinic-acid content of jowar is similar to that of rice. The reported tryptophan content of different strains of jowar varies widely, certain strains having nearly as high a content of the aminoacid as is found in rice while certain others have low values as in maize (Carpenter and Kodicek 1950). Both jowar and maize have, however, one common feature with regard to their aminoacid composition—namely, a high content of leucine. Elvehjem (1956) reported that the dietary supplementation of leucine at 1% level caused retardation of growth in rats subsisting on low-protein diets (9% casein), but that such growth retardation was not observed if the dietary protein intake was raised to 18%. The average daily protein intake in the dietaries of the pellagrins investigated here was of the order of 45 g (9% protein), the protein being mainly derived from cereals including jowar. The possible role of aminoacid imbalance resulting from relative excess of leucine in the pathogenesis of pellagra was investigated, and the preliminary results are described here.

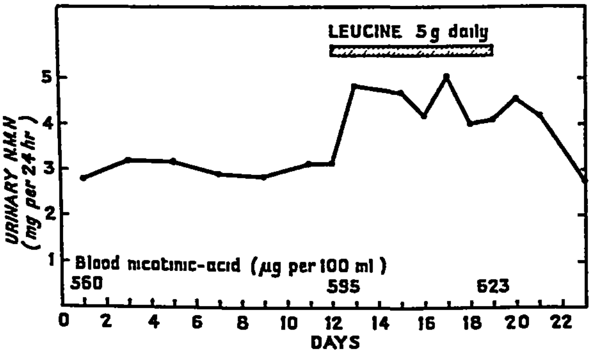

Fig 1—Effect of supplementation with leucine on urinary N.M.N excretion in a healthy subject.

Experimental

Effect of Administration of Leucine on Urinary Excretion of N-methyl Nicotinamide (N.M.N) in Healthy Volunteers and in Pellagrins

2 normal healthy male subjects were put on a basal diet providing roughly 10% protein, and their urinary N.M.N excretion was determined daily by the method of Carpenter and Kodicek (1950). The basal diet was continued until a fairly stable level of N.M.N excretion was attained. The volunteers were then given a daily supplement of 5 g L-leucine along with one meal in a single dose, for seven days, and their urinary N.M.N excretion was determined daily. Blood-nicotinic-acid levels were determined by the method of Sweeney and Hall (1951) (with some modifications) before, during, and after leucine supplementation.

Similar studies were also carried out in 3 patients with pellagra.

To determine whether the changes in urinary N.M.N excretion brought about by leucine administration could be influenced by isoleucine, 2 other healthy male subjects were investigated. These subjects also received 5 g leucine daily for three days after the initial stabilisation period, but for four days thereafter they received 2 g of DL-isoleucine daily in addition to the 5 g L-leucine.

To facilitate the quantitative interpretation of the changes in N.M.N excretion in terms of nicotinic-acid metabolism, two healthy volunteers, who had been earlier investigated with leucine as above, received a 15 mg oral dose of nicotinic acid and the increase in their urinary excretion of N.M.N was determined.

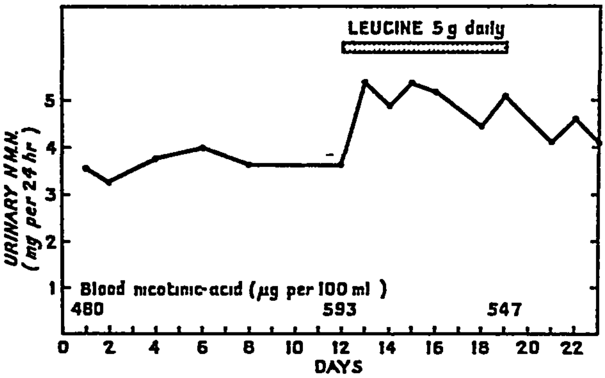

Fig 2—Effect of leucine supplementation on urinary N.M.N excretion in another healthy subject.

Effect of Isocaloric and Isonitrogenous Substitution of Rice by Jowar on Urinary N-methyl Nicotinamide Excretion

3 pellagrins were put on a basal diet providing 10% protein derived from rice and wheat, and the daily urinary N.M.N excretion was determined. After the N.M.N excretion had stabilised, rice in the diet was replaced by jowar and the daily urinary N.M.N excretion on this diet was studied. Actual analysis of the two diets revealed that the rice-wheat diet in the 3 cases provided 7·3, 7·9, and 7·6 mg nicotinic acid daily, while the jowar-wheat diet provided 7·8, 8·1, and 7·5 mg nicotinic acid daily.

Effect of Administration of Large Amounts of Leucine in Pellagrins

2 patients with pellagra were placed on a basal diet supplying 45 g of protein daily, the protein being mainly derived from jowar. After a preliminary stabilisation period these patients were given 10 g L-leucine—twice daily in 1 case and thrice daily in the other—along with their principal meals. The urinary N.M.N excretion was studied daily, and their clinical condition was carefully watched.

In this study the cases of pellagra were chronic, and the patients were not seriously ill. The patients volunteered for the investigation. We were confident that any deleterious effect of administering leucine could be corrected effectively and promptly by administration of nicotinic acid.

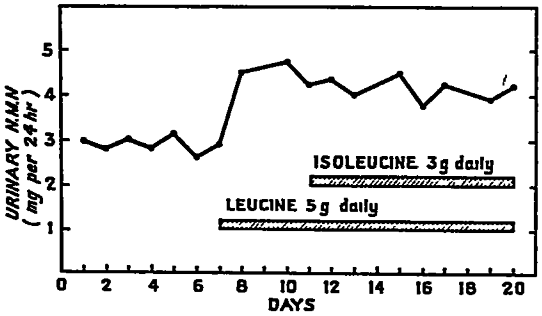

Fig 3—Effect of simultaneous supplementation with leucine and isoleucine on urinary N.M.N excretion.

Results

Effect of Administration of Leucine on Urinary Excretion of N.M.N.

The results of this study are illustrated in figs 1–3. In all subjects investigated, both healthy volunteers and cases of pellagra, urinary excretion of N.M.N. increased immediately after administration of leucine. The rise in N.M.N. excretion brought about by 5 g. L-leucine daily represented an increase of nearly 50% over the basal level. Within a few days after the withdrawal of leucine, N.M.N. excretion returned to the basal level in all cases. There were no significant changes in the blood-nicotinic-acid levels. Determination of blood-nicotinic-acid levels in the same individual on a standard diet showed wide fluctuations, the values ranging from 660 µg. per 100 ml. to 1000 µg. per ml.

The increase in N.M.N. excretion brought about by leucine did not appear to be influenced by simultaneous administration of isoleucine (fig. 3). The administration of isoleucine did not alter the N.M.N. excretion pattern.

In the 2 healthy volunteers in whom the changes in N.M.N. excretion after administration of nicotinic acid were also studied, it was found that the administration of 15 mg. nicotinic acid resulted in an increase of urinary N.M.N. excretion of the order of 8·3 mg. and 7·5 mg. This suggests that the average increase of 1·7 mg. in N.M.N. excretion brought about by the administration of 5 g. of L-leucine reflects approximately an additional 3·5 mg. of nicotinic acid metabolised daily.

Effect of Isocaloric and Isonitrogenous Substitution of Rice by Jowar on Urinary N.M.N. Excretions

The effect of substituting jowar for rice in a typical case is illustrated in fig. 4. The replacement of rice by jowar resulted in a prompt increase in urinary N.M.N. excretion over the basal level observed in the "rice period". This increase was maintained as long as jowar was continued. After the withdrawal of jowar and the reinclusion of rice, N.M.N. excretion returned to the original low level.

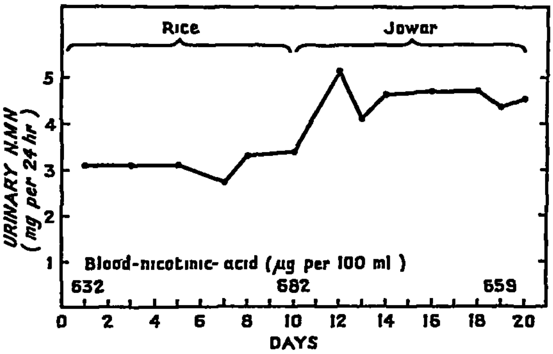

Fig. 4—Effect of replacing rice with jowar on urinary N.M.N. excretion in a patient with pellagra.

It was calculated that the daily amount of leucine contained in the jowar diet was of the order of 5·3 g. The increase in N.M.N. excretion observed was also of the same order as that obtained with 5 g. L-leucine daily. Supplementation with isoleucine did not influence the N.M.N. excretion pattern on the jowar diet.

Effect of Administration of Large Amounts of Leucine in Pellagrins

In the course of the studies, 5 g. L-leucine daily was administered to 4 patients with pellagra for seven days. This was not associated with any appreciable effects on the clinical picture. The clinical features in 2 other cases in which larger amounts of leucine were given daily were as follows.

Case 1.—The patient was admitted with classical extensive skin changes, oral manifestation of vitamin-B-complex deficiency, and diarrhœa. On admission, apart from a feeling of anxiety, he did not seem to be mentally abnormal. He answered questions promptly and correctly. He continued in this state for four days, during which he was maintained on the basal diet to attain a stable level of N.M.N. excretion. On the fifth day he was given 30 g. of L-leucine in divided doses of 10 g. each at six-hourly intervals. Towards the end of this day the patient was found to behave in an agitated manner, to become incoherent in his talk, and to exhibit delusions of grandeur. The periods of excitement were found to alternate with short periods of severe depression. An additional dose of 10 g. of L-leucine was administered next morning, and by noon the patient became uncontrollable and violent. At this stage leucine was discontinued and he was given nicotinic acid intramuscularly. Within forty-eight hours after the initiation of nicotinic-acid therapy the patient's mental state had reverted to normal.

Case 2.—On admission the patient exhibited the classical skin changes and severe glossitis and had diarrhœa. He appeared alert and answered questions intelligently; he did not show mental changes. He was placed on the basal diet, and after the period of stabilisation he was given 20 g. L-leucine daily in divided doses of 10 g. each along with the principal meals. Leucine administration was continued for sixteen days and was then stopped.

Unlike all other cases of pellagra seen by us, in which some clinical improvement results from admission to hospital, even on the basal diet without nicotinic-acid supplementation this patient did not improve clinically, but there was no evidence of worsening of the skin condition or glossitis. Three days after leucine was started, the diarrhœa became more severe and the patient complained of insomnia. On the sixth day the patient became severely depressed and apprehensive, his answers to questions were no longer prompt. When leucine was stopped on the sixteenth day the patient seemed slightly disoriented. Three days after cessation of leucine administration, his mental condition became suddenly worse. He became violent with paranoid delusions and had to be forcibly restrained; his speech was incoherent. At this stage treatment with nicotinic acid was initiated and within forty-eight hours the mental condition returned to normal.

The urinary excretion of N.M.N. was followed throughout the period. Immediately after leucine administration was started there was an increase in N.M.N. excretion, which was maintained throughout the period of leucine supplementation. Three days after leucine was discontinued, when the patient's mental condition had worsened, N.M.N. excretion was still at the same high level as during the period of leucine administration. It was, however, noticed that the increase in the level of N.M.N. excretion brought about by the feeding of 20 g. L-leucine in this case was not significantly greater than the increase observed with 5 g. L-leucine in the healthy subjects and other cases of pellagra.

During the period of leucine administration, the patient lost nearly 2·5 kg. body-weight. Within three days after leucine was stopped the weight loss was arrested, and thereafter the patient started gaining weight.

Discussion

While pellagra has long been known to be associated with maize consumption, in the present study the disease has been found to be related to the consumption of the millet "jowar" (*Sorghum vulgare*). The increase in urinary N.M.N. excretion brought about by the replacement of rice by jowar suggests that the greater prevalence of pellagra in jowar-eaters than in rice-eaters may not be attributable to deficiency in tryptophan or poor availability of its nicotinic acid. It has been shown in the present study that the administration of leucine brings about increased urinary N.M.N. excretion. This finding appears important since both maize and jowar have a high leucine content.

The precise significance of the increase in urinary N.M.N. excretion brought about by leucine requires elucidation. This increase is unlikely to be due to greater availability of nicotinic acid, because both maize and jowar, which are rich in leucine, have been associated with increased prevalence of pellagra. Apparently the aminoacid imbalance caused by relative excess of leucine in diets which are marginal with regard to protein may result in depletion of nicotinic acid from the tissues. The exact role of leucine in nicotinic-acid metabolism needs further investigation.

The increase in N.M.N. excretion brought about by supplementation with 5 g. of L-leucine daily would roughly correspond to the metabolism of an additional 3.5 mg. nicotinic acid daily. In diets which are already marginal with regard to nicotinic acid, this may be an important factor.

It would be premature to draw conclusions from these studies as to the role of leucine in the pathogenesis of pellagra. Case 2, in whom the effects of large doses of leucine was investigated, lost nearly 2.5 kg. body-weight in a fortnight during which leucine was administered. This possibly suggests that the increase in N.M.N. excretion brought about by leucine may not be a specific effect of leucine on nicotinic-acid metabolism, but reflects increased tissue catabolism due to the aminoacid imbalance. On the other hand of 6 subjects—2 healthy and 4 pellagrins—in whom the effect of leucine was investigated, only 2 with pellagra (including case 2) showed reduction in body-weight; in the remainder the increase in urinary N.M.N. excretion was associated with a stationary body-weight.

Summary

Oral administration of 5 g. L-leucine daily brought about an increase in urinary excretion of N-methyl nicotinamide excretion both in healthy subjects and in patients with pellagra. This increase was not influenced by isoleucine.

Isocaloric replacement of rice by jowar brought about an increase in the urinary N-methyl nicotinamide excretion in healthy subjects and in patients with pellagra. This increase also was uninfluenced by isoleucine.

Oral administration of 20–30 g. L-leucine daily to 2 patients with pellagra was associated with temporary deterioration of their mental condition, which was reversed when leucine was discontinued and nicotinic acid was administered.

We are grateful to Messrs. Hoffman La Roche, Basle, Switzerland, for their generous gift of leucine, used in this study, to Mr. S. N. Jagannathan for the blood-nicotinic-acid estimations and Mr. C. M. Manuel for technical assistance, and to the Director of Medical Services, Andhra Pradesh, and the medical officers of the Osmania General Hospital for their cooperation.

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Preliminary Communication

SALICYLATE-INDUCED FALL IN PLASMA PROTEIN-BOUND IODINE IN HYPERTHYROIDISM

PREVIOUS work from this laboratory has demonstrated a pattern of metabolic changes produced in normal subjects by a large single dose of sodium salicylate by mouth.[1] This pattern was associated with a fall in plasma protein-bound iodine (P.B.I.) within two hours.[2] A fall in plasma-P.B.I. after long-continued administration of salicylate in therapeutic dosage has also been shown in rats and man.[2] Similar results were reported by Austen et al.[3]

The mechanism of these changes has been discussed elsewhere.[2 4] There is no evidence of a direct effect on the thyroid,[3] although the interference of salicylate with goitre-formation in thiouracil-treated rats indicates that it suppresses production of thyroid-stimulating hormone.[4] Analogy with the fall in P.B.I. after administration of dinitrophenol to rats[5] suggests that salicylate interferes with the normal feedback mechanism—possibly situated in the hypothalamus—which controls the circulating level of thyroid hormone.[6]

We have now studied the effect of salicylate on the raised level of plasma-P.B.I. in hyperthyroid patients.

METHODS

Observations were made on eight patients who had had no treatment beyond rest and sedation in hospital.

The diagnosis of hyperthyroidism was confirmed by the usual investigations—uptake of ^{131}I, basal metabolic rate, and plasma-P.B.I. After a preliminary period of 3–8 days, salicylate was administered orally as calcium acetylsalicylate in divided 4-hourly doses between 10 A.M. and 10 P.M. to a total of 6–8 grammes a day. Fasting blood-samples were taken daily before, during, and after the period of salicylate administration.

Plasma-P.B.I. was determined by a modification of the method of Acland.[7] The finding of Austen et al.[3] that salicylate does not interfere with determination of P.B.I. was confirmed by direct addition of salicylate to plasma and also by addition of salicylate at a level of 70 mg. per 100 ml. to the washed precipitate before ashing. The method described by Trinder[8] was used for the determination of the plasma-salicylate in the same samples.

Measurements of thyroid secretion-rate were carried out after therapeutic doses of ^{131}I in three other hyperthyroid patients, using the technique of Goldsmith et al.[9] The administration of carbimazole 30 mg. 8-hourly prevented the reabsorption of ^{131}I. Serial counts over the thyroid were made with a collimated scintillation detector and the counts were plotted on a semilogarithmic scale (fig. 2).

RESULTS

The effect of salicylate on the first hyperthyroid patient (A) is shown in fig. 1.

From an initial plasma-P.B.I. level of 14.0 µg. per 100 ml. there was a progressive fall to 10.6 µg. by the 4th day of salicylate administration (6 g. per day) when the plasma salicylate-level had reached 41 mg. per 100 ml. Withdrawal of the drug

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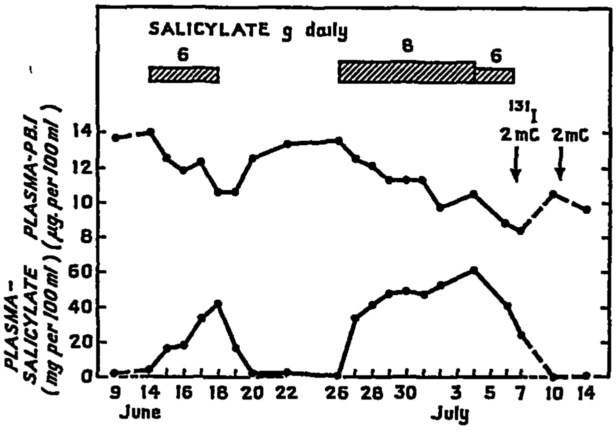

Fig 1—Depression by salicylate of elevated plasma-P B I in hyperthyroidism The patient (A) is a woman of 50

was associated with a rise of the plasma-P B I to 12 6 µg per 100 ml after 2 days and to 13 4 µg after 4 days and with rapid fall in the plasma-salicylate to zero After 8 days salicylate was readministered in doses of 8 g per day The plasma-P B I fell to 9 8 µg per 100 ml by the 6th day when the plasma salicylate reached 53 mg per 100 ml A fall to 9 0 µg occurred by the 10th day, after which salicylate was discontinued and a dose of 2 millicuries of ^{131}I was given on the same day The following day the plasma-P B I was 8 6 µg 4 days later the level had risen to 10 8 µg and the plasma-salicylate had fallen to zero later that day a further 2 millicuries of ^{131}I was given

Similar falls have been noted in seven other hyperthyroid patients given salicylate in a dosage of 6 g per day for 4 days

The data from these patients are summarised in the table The values indicate a mean fall in the plasma-P B I from 13 8 µg per 100 ml to 11 5 µg after one day and to 9 6 µg after 4 days of salicylate administration by which time the mean plasma-salicylate had reached 29 mg per 100 ml Plasma-P B I values on the 2nd and 3rd days of salicylate administration lay between those for the 1st and 4th days, confirming the progressive fall shown by patient A (fig 1) Two days after withdrawal of salicylate the mean plasma-P.B I level had risen to 11 5 µg

The effect of salicylate on thyroid secretion was studied in three other patients after therapeutic doses of ^{131}I, and fig 2 shows the result in one of them

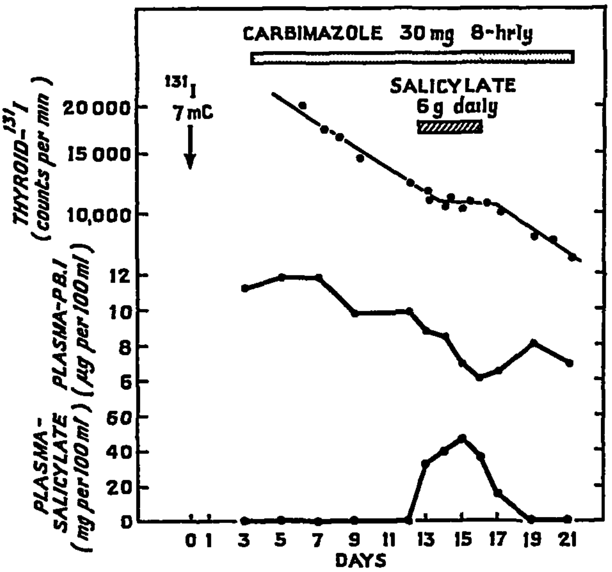

Fig 2—Depression by salicylate of elevated plasma-P B I and thyroid secretion in hyperthyroidism The patient is a woman of 48

During the preliminary period of carbimazole administration, the plasma-P B I fell from 12 0 µg per 100 ml to 10 µg, and a further sharp fall to 6 2 µg took place after the administration of salicylate Within 48 hours of the administration of salicylate the rate of decay of thyroid ^{131}I slowed indicating a fall in thyroid secretion After the withdrawal of salicylate, the rate of fall in thyroid ^{131}I increased and the plasma-P B I rose to 8 2 µg Similar results were obtained in the other two patients

DISCUSSION

The data reveal that salicylates depress the high level of plasma-P B I in hyperthyroid patients In normal subjects such a fall in the circulating hormone level has been attributed to an interference with the feedback mechanism[2 3 5] Comparison with a normal group indicates a similar proportional effect on the plasma-P B I by salicylate[10] These observations suggest that the feedback mechanism controlling the circulating thyroid hormone is as sensitive to salicylate in hyperthyroidism as it is in normal subjects

The reduction of thyroid secretion caused by salicylate in three patients with hyperthyroidism resembles the reduction seen in normal subjects, as reported by Wolff and Austen[4] Other studies have shown similar effects and time-relationships after the use of Lugol's solution in hyperthyroid patients[9 11] These changes suggest some interference with thyroid-stimulating hormone activity—either a reduction in secretion, an inhibition of its effect on the thyroid, or both[9 11] This could mean that, in hyperthyroidism, the thyroid is partly under the control of the pituitary However, this does not accord with a recent report describing two cases in which hyperthyroidism persisted after hypophysectomy[12]

The fall in plasma-P B I appears to have preceded the effect on thyroid secretion This may indicate the operation of an additional mechanism, particularly as there was a consistent, though significantly smaller, fall in plasma-P B I after salicylate in six hypothyroid subjects maintained on desiccated thyroid when compared with a normal group[10] A striking fall in plasma-P B I has also been observed in thyroxine-maintained thyroidectomised rats given salicylate[13] Until recently it has not been possible to demonstrate interference with protein-binding of thyroxine by salicylate in vitro, but Ingbar[14] has now

EFFECT OF SALICYLATE ON PLASMA PROTEIN-BOUND IODINE IN HYPERTHYROIDISM

Subject	Age	Plasma-P B I (µg per 100 ml)				Plasma salicylate (mg per 100 ml)†
		Before salicylate*	Period of salicylate administration		2 days after withdrawal of salicylate	
			1 day	4 days		
A	52	13 9	12 5	10 6	12 6	41 0
B	37	14 4	12 8	11 0	12 3	20 0
C	59	10 1	9 0	6 0	6 3	40 0
D	42	12 9	9 7	9·0	9 2	22 0
E	39	15 0	13 0	9 6	14 0	27 0
F	26	15 3	12 6	11 8	14 4	25 0
G	36	12 7	9 5	8 2	12 0	20 0
H	30	15 9	12 7	10 5		37 0
Mean		13 8	11 5	9 6	11 5	29 0

* Mean of two values during preliminary period of observation
† After four days salicylate administration (6 g per day)

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10 Hetzel, B S , Good, B F , Wellby, M L , Charnock, J S Proceedings Fourth International Goitre Conference (to be published) 1960
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shown that it can occur. Clearly more than one mechanism may be operating in this action of salicylate on plasma-P.B.I.

Our subsequent observations indicate that Lugol's solution causes a similar rapid fall in plasma-P.B.I. which takes place before the effect on thyroid secretion previously shown.[9, 11] In fact, in three hyperthyroid patients given both drugs, the rate of fall in plasma-P.B.I. after salicylate closely resembled that seen after Lugol's solution. On the other hand, no effect on the sleeping pulse-rate has been noted with salicylate, whereas after Lugol's solution it consistently fell. This may be related to the metabolism-stimulating effect of salicylate,[1] still evident in hyperthyroidism. This limits the possible value of salicylate as therapy in hyperthyroidism. Further investigations with related drugs free from the hypermetabolic and other undesirable side-effects of salicylate are now being undertaken.

SUMMARY

In ten patients with hyperthyroidism, salicylate in doses of 6–8 g. per day consistently reduced the plasma protein-bound iodine. The action resembles that of Lugol's solution, but salicylates do not affect the sleeping pulse-rate.

We are indebted to the honorary physicians of the Royal Adelaide Hospital and the Queen Elizabeth Hospital for access to patients under their care. This investigation was supported by the National Health and Medical Research Council of Australia with whole-time grants to two of us (M. L. Wellby and J. S. Charnock).

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New Inventions

NEW, PULSE-GIVING, HYDRAULIC PUMP FOR EXTRACORPOREAL CIRCULATION

DESPITE the increasing number of publications on extracorporeal circulation no essential changes in the pumping principles have been described. All designs have been adapted from pumps previously used in industry ('Zigma' pumps, roller pumps, plate pumps, and membrane pumps). In these pumps the blood is propelled and reflux prevented by means of a direct mechanical effect on the tube conveying the blood through the pump.

In order to avoid the disadvantages of such pumps, a pump was constructed which ensures a pulsatile blood-stream without significant destruction of the blood-corpuscles.

In essence the pump consists of a tube which is rhythmically compressed and expanded by hydraulic action, while valves inside both ends of the tube ensure that the blood passes through the tube in one direction only.

The pump chamber is shown diagrammatically in fig. 1. A wide plastic tube (1) is enclosed in a rigid chamber (2) completely filled with liquid (5). Valve boxes (3 and 4) are inserted, watertight, into each end of the chamber by means of interior connecting pieces on to which the plastic tube is fitted. By means of a motor-driven piston (6) in the bottom of the chamber the volume of the rigid chamber is rhythmically decreased and increased, resulting in equivalent compression and expansion of the plastic tube. The volume of blood which, in this way, is rhythmically pumped out of and into the tube will be exactly the same as the known volume change of the chamber caused by the movement of the piston, the valves being constructed as direct-current, horizontal, pressure-loaded ball valves impeding any reflux. The motive force is supplied by a three-phase A.C. motor (0.5 H.P.) rotating with a constant maximum number of revolutions. By means of a special gear, both the stroke-volume and the frequency of strokes can be varied. The stroke-volume can be varied continuously from nil to 70 ml. per stroke; when the stroke-volume is increased the piston continues to start from "zero" position. The frequency can be changed continuously from 20 to 150 strokes per minute, and accordingly the total minute-volume can be varied from nil to about 10 litres. The stroke-volume, the frequency, and the minute-volume can be read on a single scale.

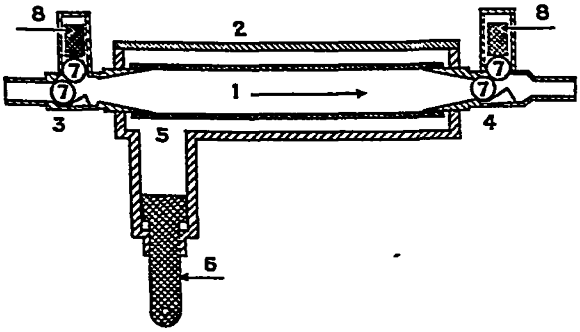

Fig. 1—Diagram showing pump principle. 1, tube (1 in. internal diameter); 2, chamber; 3 and 4, valve boxes; 5, liquid-filled space; 6, piston; 7, perspex balls; 8, weights keeping balls in position.

The valve boxes and the valve balls are made of 'Perspex'. The other parts of the pump which come into direct contact with the blood are plastic tubes.

The present pump was constructed for use in connection with any type of oxygenator. In this case a screen oxygenator was used (Mark III, Gibbon type). Therefore, three pump chambers were applied with a reciprocal mechanical coupling of the pumps in the following way.

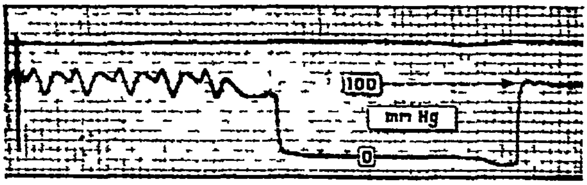

Fig. 2—Electrocardiogram and pressure-curve from femoral artery during perfusion under cardioplegy: registration by a condenser manometer through a 100 cm. Cournand heart catheter no. 8, introduced about 5 cm. above the inguinal ligament.

Pump no. 1 acts as an arterial pump. Pump no. 2 transports the blood from the venous reservoir to the top of the oxygenator. These two pumps are mechanically coupled and both transport exactly the same quantity of blood. By means of a single manipulation one of the two pumps can be stopped while the other pump continues to work independently. Pump no. 3 transports to the top of the oxygenator the 2 litres of blood per min. necessary to maintain the blood-film on the screens of the oxygenator. In order to avoid 2 litres of excess blood constantly passing through the oxygenator, pump no. 3 is mechanically connected with pump no. 2 in such a way that pump no. 3 transports only the supplementary amount necessary for the maintenance of the blood-film on the screens of the oxygenator, and pump no. 3 is automatically disconnected when pump no. 2 transports 2 litres of blood or more.

In constructing this pump system special care was taken to make the transport of blood as gentle as possible in order to reduce hæmolysis as much as possible. This was achieved by choosing suitable material, by making the pump tubes (fig. 1) so wide that even a maximum stroke-volume will not

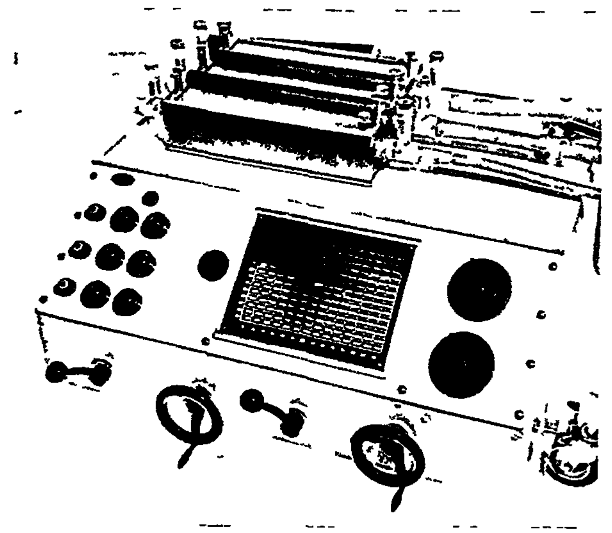

Fig 3—The complete heart pump (length 700 mm, depth 640 mm, height 700 mm.)

cause contact between the inner walls of the pump tubes, and, finally, by reducing the contact surface of the valve balls against the valve seatings to a minimum. In five experiments hæmolysis did not exceed 4 mg. of free hæmoglobin per 100 ml. of plasma (experimental conditions: flow 6 litres per minute, duration 30 minutes, total blood-volume 1 litre per experiment, temperature of blood 37°C. The blood was citrated bank blood kept for a week in siliconised bottles at 4°C).

Fig. 2 shows the pulsation in the femoral artery during perfusion of a dog under potassium-induced cardioplegy through a 100 cm. Cournand heart catheter no. 8, introduced about 5 cm. above the inguinal ligament.

Fig. 3 shows the complete heart pump. The three pump chambers are on top, and the scale for stroke-volume, frequency, and minute-volume, and the operating-handles in front.

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A STANDARD, CARTRIDGE-FORM, COTTON-WOOL AIR-FILTER FOR PRESSURE-STEAM STERILISERS

THE need for efficient air-filtration for hospital sterilisers is generally realised, but many sterilisers lack adequate filters and are merely fitted with a tube or container designed to hold cotton-wool. While sterile, non-absorbent cotton-wool, correctly used, gives safe filtration,[1] the incorrect use of cotton-wool and the use of absorbent wool or materials such as cotton-gauze gravely endanger sterilisation. The Medical Research Council working party on pressure-steam sterilisers reviewed the problems involved.[2]

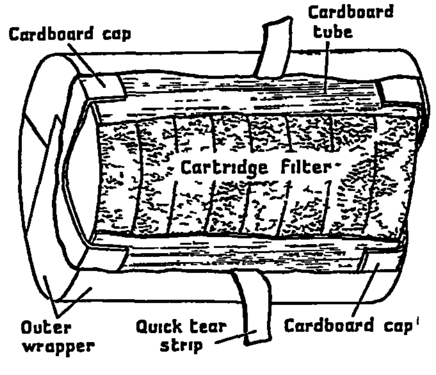

Fig 1—Diagram of structure of cotton-wool cartridge-filter

To obviate human error in the use of cotton-wool for air-filtration a standard filter, in cartridge form,[3] suitable for use with all pressure-steam sterilisers, has been evolved. It consists of eight circular layers of non-absorbent cotton-wool in a cardboard tube three inches long, capped at both ends. The unit is sealed in paper (fig. 1) and sterilised in a high-vacuum autoclave. A special filter-holder [3] is required, which should be fitted to the steriliser horizontally, at eye-level and in an accessible position. For use, the paper wrapper of the filter-cartridge is opened by pulling the quick-tear strip and discarded, together with one end-cap. The open end of the tube is placed in the mouth of the filter-holder, and the other end-cap is removed, when the filter can be pushed through the tube into the holder (fig. 2). The tube is then discarded and the lid of the holder shut. The only part of the filter to be contaminated is the outer face, the inner surface remaining completely untouched. The interior of the filter-holder tapers to a knife-edge seal, above the perforated base-plate, to ensure an air-tight fit when the filter is pushed home. The air-seal is automatically reinforced by compression of the cotton-wool, on vacuum-release. The filter is changed daily and is left in the holder after use, to prevent contamination of the air-line.

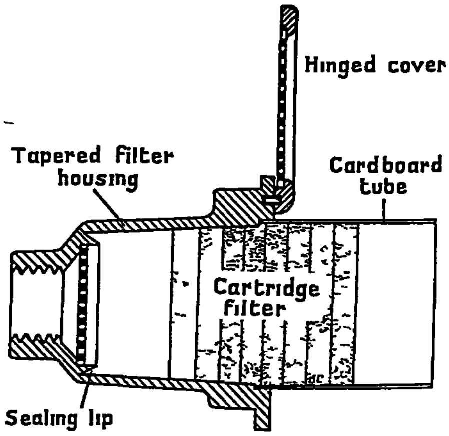

Fig 2—Method of inserting filter into filter-holder. The cover of the filter-holder is lowered once the filter has been pushed home and the cardboard tube is removed

The test-apparatus and autoclave previously described [1] were, by courtesy of Manlove, Alliott & Co., again used in a series of over 80 tests. A heavily contaminated atmosphere was obtained by spraying a broth culture of *Chromobacter prodigiosum* from an atomiser into a biscuit-tin fitted over the mouth of the filter-holder. On vacuum release, this air was sucked through the air-line. Controls, without the filter, all yielded over 1000 colonies per plate (nutrient agar). All tests with five or more layers of cotton-wool showed effective filtration (no growth). Four layers allowed occasional bacteria to pass, yielding a few plates with one or at most two colonies. The final thickness of filter was determined by adding a 50% safety-margin to the minimum effective thickness (five layers).

It is hoped that this filter, by ruling out the use of the wrong type of cotton-wool, by ensuring its sterility, and by giving uniform and safe air-filtration, will make a real contribution to the practice of hospital sterilisation.

I wish to thank Vernon & Co. Ltd., of Preston, and Steritec Ltd., of Nottingham, who have collaborated in evolving the 'Sterifilta' filter and filter-holder, respectively, Dr. J. C. Kelsey for suggesting the use of *Chr. prodigiosum* as the test-organism, and Mr. C. A. Durrant, F.I.M.L.T., for help with the bacteriology.

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[2] M.R.C. working party report on pressure-steam sterilisers. *ibid.* 1959, i, 425.

[3] Provisional patent 10587/59.

Reviews of Books

Blindness in West Africa

F. C. RODGER, M.D., CH.M., F.R.C.S., research professor of ophthalmology, Aligarh University, India; director, ophthalmological survey, Royal Commonwealth Society for the Blind London H. K. Lewis (for Royal Commonwealth Society for the Blind) 1959 Pp 262 75s

IN parts of tropical Africa and the Americas onchocerciasis is a cause of blindness seldom found elsewhere. Dr Rodger and his assistants worked on this problem for four years in Northern Ghana, Northern Nigeria, and the Cameroon Highlands, and this book records their findings which are of great interest and importance, and the result of painstaking labour. Dr Rodger is to be congratulated on an achievement which will, we hope, stimulate not only other workers but also Governments.

The introduction says the book was written so that interested lay persons could appreciate parts of it this may be a mistake for it is often as hard for a man to write for two publics as it is for him to serve two masters The determination of the incidence of blindness will arouse comment. The methods used are not described, but it is stated that " a general picture of the incidence of blindness in West Africa will emerge from the analysis now to be given " Many villages and townships were visited and perhaps a more precise and valuable picture would have emerged from a study of a smaller sample in greater detail.

The section on onchocerciasis is full and the detailed descriptions of its syndromes are very valuable, though not all workers will agree that onchocerciasis alone is responsible for all these conditions Thus, there is resistance against diagnosing punctate keratitis as onchocercal even when conjunctival biopsies are positive, but with " chronic, non-specific uveo-retinitis the association with an anterior lesion of onchocerciasis points to the diagnosis " Elsewhere, regarding onchocercal chorioretinopathy, it is pointed out that " it is remarkably difficult to distinguish between this lesion and a chorioretinitis due to syphilis and tuberculosis "

The method of assessing the individual density figure for infection is also open to criticism, because an arbitrary score is given for finding onchocercal microfilariæ in different parts of the body. It is perhaps unfortunate too that the Southern Cameroons, where onchocerciasis is highly endemic, but where the climate is very different from the Northern regions, was not included in the study

The reviews of the literature reveal that many of the subjects *remain highly controversial*, but this book stands out as a lively and *helpful contribution* to the forum

Family and Class Dynamics in Mental Illness

JEROME K. MYERS, associate professor of sociology, Yale University; BERTRAM H ROBERTS, late assistant professor of psychiatry, Yale University New York John Wiley London *Chapman & Hall*, 1959 Pp 295 56s

THIS interesting book describes the second and rather less auspicious part *of an extensive* sociopsychiatric survey In the *now celebrated* earlier part, Professor Hollingshead and Professor Redlich[1] used the census method to demonstrate that the prevalence, type, and treatment of psychiatric disorder was related to class structure This study examines 50 families in detail to discover different social and dynamic factors at work between different classes (in which it is successful) and the relationship of social mobility to psychiatric illness (in which it is a little less successful)

In brief, class-5 illness tended to arise in a troubled setting, much preoccupied with material survival, where Father acted as a powerful uninterested authority figure and where conflicts were acted out in antisocial ways In class 3, though Mother was more dominant, control of the children was better and family control was more [illegible] [illegible] and [illegible] predominated here. Schizophrenics of [illegible] showed a [illegible] life pattern and were viewed as "different" from the others, but on the other hand they were subjected to more pressures and stresses at all levels than the neurotics. It was suggested that, coming from homes of more disturbed parents, and receiving less affection than [illegible], [illegible] with the more disturbed parent (usually Mother) and followed the difficult situation by withdrawing from [illegible] Much valuable information is also given on parental and sibling [illegible], sexual difficulties, and [illegible] symptomatology

Although this book maintains the professional's extremely high standard of scholarship and presentation, it is of [illegible] value for several reasons [illegible] [illegible] classes 3 and 5 only, [illegible] and [illegible] are so [illegible] as to [illegible] explanation of the findings. It is also limited to treated cases, to [illegible] ages of 22-44, and to those willing to cooperate. The data, furthermore, were retrospective, and there were no controls These defects, however, are understandable in the face of the immense practical difficulties in the way of this type of research The next stage in developing psychiatric work is to make quantifiable observations in the home setting, and this excellent study and "exploratory" one as the authors admit will be a signpost to future workers

The Chemistry of Heredity

S ZAMENHOF, PH.D., associate professor of biochemistry, Columbia University, New York Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1959 Pp 100 24s

COMPRESSING what is known of the chemistry of heredity into 80 pages while retaining some semblance of cohesion, is a task not to be undertaken lightly, and Dr Zamenhof may be said to have rushed in where other investigators have remained at the bench

He introduces his monograph with the surprising comment that " The very thought of reading a book about the Chemistry of Heredity is likely to encounter a great deal of resistance The word ' Chemistry ' is often inimical and reminds one of a lot of difficult or boring moments in one's school days " This may explain why he has adopted a style of lightweight simplicity which seldom attempts to penetrate below the surface, and why he occasionally introduces exclamatory comments and often italicises words and phrases

Nucleic acids, mutation, and cytoplasmic inheritance are among the subjects fleetingly but sensibly discussed The chapter on nucleic acid, although too brief, is clear and up to date and it is apparent that the author, as a distinguished investigator who has made notable contributions to the subject, is a capable critic and interpreter of the recent scientific literature. The often neglected work of Griffith, which preceded the definitive studies of Avery, is admirably emphasised in the account of transformation, and this section is one of the best in the book. The section on hereditary defects in man is contained in 8 pages. Alkaptonuria, albinism, galactosæmia, and sickle-cell anæmia are among the subjects that are discussed rather too briefly.

A well-chosen bibliography of 185 articles is the most valuable asset of this small monograph, one of a series of American Lectures in Living Chemistry. The book, well produced but expensive, may serve as an accurate introduction to a subject which urgently requires a more rigorous treatment.

Bibliography of Cancer Produced by Pure Chemical Compounds

A Survey of the Literature up to and including 1947. OTTO NEUBAUER, M D, formerly professor, Munich University. London Oxford University Press 1959 Pp 604 42s.

IN a foreword, the late Sir Ernest Kennaway remarks that " at the present time, the progress of every science tends to be impeded by the accumulation of its own literature . . .". Probably of no other branch of science is the statement more true than of cancer research The result of the late Professor Neubauer's courageous undertaking in cataloguing, indexing, and classifying what is virtually the major part of experimental cancer research up to 1947 is a unique achievement For apart from the thoroughness with which references were pursued, and the tenacious accuracy with which they are presented, the bibliography is more comprehensive than anything that has been attempted in this subject since the early exhaustive reviews of tar cancer by Woglom (1926) and Seelig and Cooper (1933) The confluence and interplay of the various scientific disciplines in cancer research is clearly shown

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[1] See *Lancet*, 1958, ii, 888

The work consists of two main parts—an author index and a subject index, together with a list of tumour sites The subject index includes an English translation of the titles of papers which are in another language This part is divided into 32 sections which deal with the various parameters involved in carcinogenesis, with the chemical and physical nature of the agents, their mode of administration, their metabolism, their effects on the organism, and intrinsic and extrinsic influences on their course of action The sections are subdivided according to the chemical nature of the carcinogen, aromatic hydrocarbons, azo-compounds, &c., and in such subdivisions the papers are arranged in chronological order, bringing out the history of the development of the subject. It was the era of the aromatic hydrocarbons

Since 1947 many agents and modes of tumour production have been discovered—e g , films of high polymers, alkylating agents, certain alkaloids, and such bizarre carcinogens as tricycloquinazoline and 4-nitroquinoline-N-oxide, not to mention intermittent anaerobiosis (We hope the bibliography will be supplemented with such new data at intervals in the future) A minor criticism might be directed against the representation and inclusion of heated fats and oils, non-ionising radiation, and certain virus preparations as pure chemical compounds

Parasites and Parasitic Infections in Early Medicine and Science

R HOEPPLI, M D , D SC , formerly professor of parasitology, Peking Union Medical College Singapore University of Malaya Press 1959 Pp 526 63s

AFTER a lifetime of valuable contributions to parasitology, the distinguished author now brings together in this attractive volume the fruits of many years' historical studies Although much of the material is Chinese, contributions are also included from Borneo, Malaya, Fiji, Tahiti, and Europe, so that part I is an extensive account of the history of parasitology from ancient times to the middle of the 17th century, and in part III some publications as late as the 19th century are included Part II deals with special parasitological subjects, such as malaria, dysentery, scabies, and leeches in Chinese medicine, Chinese anthelmintics, and the remarkable habit of eating lice An interesting appendix discusses the part played by parasites in history, in which syphilis, trypanosomiasis, malaria, hookworm disease, and schistosomiasis are included Not the least valuable items are the references to the literature at the ends of each section and in the footnotes The Chinese characters have been written by Mr Choo Yew-Wai

Professor Hoeppli refers to " the ticklish question whether Adam and Eve in Paradise had lice ", and to the writer in *The Gentleman's Magazine* for 1746, quoted also by Zinsser in his *Rats, Lice and History*, who remarked, with all the charm of the outlook of that time, that " we can hardly suppose that it (the louse) was quartered on the neatest pair (if we may believe John Milton) that ever joined hands And yet, as it disdained to graze the fields or lick the dust for sustenance, where else could it have had its subsistence ? " And yet if, as Hoeppli tells us, Herodotus recorded the habit of eating lice, which is still " comparatively widespread today ", can we blame this " neatest pair " if they did not disdain to eat companions who themselves disdained to lick the sustaining dust ?

But this is a lighter side of this careful and well-documented book It abounds in information and shrewd observation, and there are 23 plates, which include the first illustrations of *Cysticercus pisiformis*, a tapeworm, and an itch-mite, as well as figures of other parasites and photographs of the methods of spirit-doctors

Isotopic Tracers (2nd ed London University of London, Athlone Press 1959 Pp 524 52*s* 6*d*) —The great value of the first edition of this book, by Dr G E Francis, Dr W Mulligan, and Prof A Wormall, was that it was written by a team of biochemists in touch with medical and veterinary matters They knew that medically qualified research-workers often have limited experience in physics and mathematics, and they knew the kind of problems in which they were interested In the five years since the first edition there has been much expansion in the application of tracer techniques, and many changes in the practical details The sections on instrumentation and practical methods have been considerably expanded, and part II of the book gives a list of exercises that could be used for an " instructive and interesting practical isotope course " The greater part of the book is taken up with description of the available isotopes, both stable and radioactive, their properties, preparation, and measurement, and the preparation of labelled compounds is fully dealt with Many examples of the use of isotopic tracers in biological and medical research are discussed The importance of understanding the hazards of using radioactive isotopes is emphasised, and practical precautions against unnecessary exposure are set out Fourteen short appendices provide useful notes on the characteristics of available isotopes and where they can be obtained, on terminology, and on some practical techniques ; some mathematical information is also included Useful bibliographies are provided at the end of each chapter Any doctor preparing to embark on isotope-tracer research should begin by studying this well-produced and low-priced book, and all users of these techniques will find it a valuable handbook

Blood Clotting Factors (Proceedings of the 4th International Congress of Biochemistry, Vienna, 1958, symposium X London and New York Pergamon Press 1959 Pp 254 70*s*) —This is one of 15 volumes recording the proceedings of what must have been a mammoth conference Edited by E Deutsch, it contains 16 articles in English and 5 in German on biochemical researches concerned with blood-clotting factors The papers vary in length from 25 lines to 37 pages, a few of them have summaries They are mostly very technical and only of interest or even intelligible to those engaged in this work, and many of them are devoted to progress reports about attempts to purify or isolate clotting factors—for example, the paper by Brinkhous and Wagner on the anti-hæmophilic factor A paper by Gross, Löhr, and Waller, of Marburg, strikes a new note by exploring the carbohydrate-metabolising enzymes of platelets and suggesting that Glanzmann's thrombasthenia is associated with a deficiency of these enzymes A J Quick reiterates his views on the properties and formation of tissue-thromboplastin and its relation to plasma-thromboplastin He also points out that erythrocytes contain a phospholipid clotting agent which can be applied to the diagnosis of hæmophilia B (Christmas disease) A paper by Biggs and Bidwell, of Oxford, on the kinetics of blood-thromboplastin formation emphasises the difficulties of interpreting results while testing systems are still crude Lorand and coworkers at North Western University, Illinois, have produced a brand-new factor, " fibrin-stabilising factor " This volume may be a useful reminder to those who attended the conference, but we doubt whether it fully justifies the trouble and expense devoted to its publication, since any work that is not purely transitory will surely be published sooner or later in medical or biochemical journals

THE LANCET

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Mucoviscidosis in Adults

OUR children's diseases are growing up at last—a reflection perhaps of better pædiatric management as well as of improved diagnostic methods in adult life Thus, symptoms and signs in adults reminiscent of the childhood manifestations of mucoviscidosis (or fibrocystic disease) have led several workers to search for this condition in adult hospital populations; and KOCH, of Giessen, has now reviewed no less than 84 such cases[1] Besides the surprising frequency of the disease, several important facts emerge from his careful analysis Relatives of 41 patients showed some clinical or laboratory evidence of mucoviscidosis—a finding which suggests to KOCH autosomal dominant inheritance with a fairly high penetrance rather than a recessive mode of transmission (He does not consider the possibility of *formes frustes* in heterozygotes[2,3]) Many of his patients and their relatives, moreover, also had peptic ulceration —a recognised but exceedingly rare complication of the illness in childhood This prompted him and his associates to investigate five groups of adults 32 healthy university students, 35 cases of gallbladder disease with suspected pancreatic involvement, 43 patients with peptic ulcer, 88 patients admitted to hospital on account of various unrelated complaints, and 68 close relatives of the 41 mucoviscidosis patients The diagnosis was based on clinical evidence, estimation of sweat-electrolytes, and analysis of pancreatic enzymes—mainly in duodenal aspirates

Though its physiological mechanism and ætiological significance are still undecided,[4–7] the high salt content of sweat of patients with mucoviscidosis is a valuable diagnostic finding For screening purposes, so long as its limitations are appreciated, the finger-print test is a simple and attractive ward procedure[8], but for accuracy sweat must be collected in plastic bags and subjected to chemical analysis[9,10] In health sweat very rarely contains more than 60 mEq chloride, 70 mEq sodium, or 20 mEq potassium per litre—there was one instance in KOCH's survey—and higher concentrations than these were not found in the other illnesses investigated at the Giessen clinic. Pancreatic enzymes are best analysed in fractional samples; and especial attention must be paid to an unequal depression of the various enzyme activities The four estimated by KOCH were amylase, trypsin, lipase, and carboxypeptidase[11–13], and in 11 out of 18 patients with mucoviscidosis the activity of one or another was depressed This contrasts with the findings in gallbladder disease associated with pancreatitis, in which the activity of all duodenal enzymes is often uniformly low Of 43 peptic-ulcer cases the values were normal in about half, the other half had dissociated pancreatic insufficiency, carboxypeptidase activity being diminished most commonly and lipase activity only rarely (KOCH mentions a 60-year-old man with high-normal amylase and trypsin levels, almost complete absence of carboxypeptidase and lipase activity, and a raised sweat-electrolyte excretion; he had two recent ulcers on the lesser curve of the stomach and long-standing duodenal scarring)

These curious findings naturally suggest the possibility of bias in the selection of the case-material, for, as KOCH rightly observes, our diagnostic methods for the detection of mucoviscidosis are by no means foolproof On the other hand, valuable information can be had from family studies Of the 68 relatives of the 41 cases of mucoviscidosis, only 9 were entirely free from symptoms, signs, or laboratory evidence of the disease 17 of the mucoviscidosis patients and 19 of the relatives available for investigation had peptic ulceration The prevalence of peptic ulcer in families with mucoviscidosis thus appeared to be ten times greater than that in the normal population[14] Approaching this association from another angle KOCH investigated 43 unselected ulcer patients who had come to the clinic for the treatment of peptic ulcer Comparing them with the 36 ulcer cases from mucoviscidosis families he found little difference in their age and sex distribution and in the age at onset of symptoms The proportion of duodenal and gastric ulcers, however, was 25 18 in the unselected ulcer series and 31 5 among patients from mucoviscidosis families, and sweat-electrolyte disturbances were twice as common and pulmonary emphysema three times as common in the mucoviscidosis group Pancreatic-enzyme activity was related little if at all to the position of the ulcer and possible pancreatic penetration. About half the unselected ulcer cases exhibited one or more of the characteristic features of mucoviscidosis KOCH also formed a clinical impression of certain differences between peptic-ulcer patients with mucoviscidosis and those without. The former group included a high proportion of middle-aged men with duodenal ulcers who commonly had multiple ulcers, had otherwise unexplained cachexia, dehydration, low blood-pressure, and a tendency to cardiovascular collapse, and who, since a fairly early age, had had pulmonary emphysema, cyanosis, and clubbing of the fingers In these patients the characteristically raised sweat-electrolyte levels, a positive family history for mucoviscidosis, and dissociated pancreatic insufficiency often confirmed his clinical suspicion

If the emergence of mucoviscidosis from the children's ward has already yielded one surprising link with a common illness of middle and later life, others are likely to follow We have hinted at the great diversity of some of the late manifestations of the disease[7], and many may still be unrecognised Even the classical manifestations of the childhood illness tend to escape detection in adults The respiratory syndrome can become almost indistinguishable clinically from other chronic lung diseases associated with the formation of large quantities of viscid sputum (notably infective asthma)[15–17], but it is worth remembering that in mucoviscidosis secondary staphylococcal infection is said to be particularly common[9,18] This organism thrives in a medium containing a higher concentration of salt than is favoured by most bacteria, and possibly the salt-rich salivary and bronchial secretion of patients with mucoviscidosis inhibits potential competitors On the other hand, after long-continued treatment with a wide range of antibiotics other organisms—mainly proteus and pseudomonas—are now being isolated with increasing frequency, and we can certainly expect a growing incidence of monilia infection The conditions created by long-standing fibrocystic disease in the lungs are ideal for the development of cor pulmonale but even direct involvement of the myocardium cannot yet be excluded[19]

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[1] Koch, E *Germ med Mon* 1960, 5, 40
[2] Smoller M., Hsia, D Y-Y *A.M.A J Dis Child* 1959, 98, 277
[3] Childs, B Report of the 18th Pediatric Research Conference, Columbus, Ohio, 1956, p 67
[4] di Sant Agnese, P A. *Amer J Med* 1956, 21, 406
[5] Peterson E M. *J Amer med Ass* 1959, 171, 1
[6] Roberts, G B S *Lancet*, 1959, ii, 964
[7] *ibid* p 955
[8] McFarlane, J C., Norman, A P *Brit med J* 1957, ii, 274
[9] Schwachman, H., Leubner, H *Advanc Pediat* 1955 7, 249
[10] Bohn, H , Koch, E., Koch, F , Rick, W , Rauh, R. *Dtsch med Wschr* 1959 84, 1139
[11] Andersen, D H , Early, M. V *Amer J Dis Child* 1942, 63 891
[12] Nothman, M. M., Pratt, T D , Benotti, J *J Lab clin Med* 1948, 33, 833
[13] Schwachman, H. *A.M.A J Dis Child* 1956, 95, 347
[14] Doll, R *Ann Eugen* 1949, 14, 135

Of the less common features of the disease, biliary cirrhosis merits more attention than it receives at present It should be added to the growing list of causes of jaundice in the newborn, and in adolescence and adult life it must be considered as an ætiological factor in portal hypertension[20–23] In these cases bleeding from œsophageal varices is commoner than hepatic failure Electrolyte imbalance is another complication that requires the utmost care for detection, assessment, and management Patients with mucoviscidosis can lose alarming amounts of sodium, potassium, and chloride in their sweat—far more than we generally allow for in making up fluid-balance charts—and often this has to be added to other losses through diarrhœa and viewed against a background of chronic respiratory acidosis The task of maintaining balance is indeed formidable; and even minor operations provide a severe test in applied physiology[17] Steatorrhœa has long been recognised as one of the cardinal features of mucoviscidosis in childhood, but adults too deserve a second look We know too little of this common and disabling condition to dismiss the diagnosis of mucoviscidosis on the ground that routine pancreatic-function tests are negative The unusual type of inflammatory reaction reported by MARKS and ANDERSON[24] may prove characteristic Their middle-aged patient with longstanding pulmonary suppuration and steatorrhœa also had choroiditis, vitreous opacities, and enlarged submandibular salivary glands—pointers to further possible ramifications of this puzzling and perhaps not so rare syndrome

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15 Noah, J *Amer J Med* 1959, 27, 485
16 Weeks, M M , Brown, G A *Arch Dis Childh* 1958, 33, 74
17 Kulczycki, L , Craig, J M , Schwachman, H *New Engl J Med* 1957, 257, 203
18 Harford, C G *Amer J Med* 1959, 27, 490
19 Powell, L W , Jr , Newman, S , Hooker, J W *Virginia med Mon* 1957, 84, 178
20 Farber, S *Arch Path* 1944, 37, 238
21 di Sant Agnese, P A *J Amer med Ass* 1956, 160, 846
22 Craig, J M , Haddad, H , Schwachman, H *Amer J Dis Child* 1957, 93, 357
23 Norris, T St M *Proc R Soc Med* 1957, 50, 507
24 Marks, B L , Anderson, C M *Lancet*, Feb 13, 1960, p 365

Staphylococci in the Family

No other microorganism can compare with the staphylococcus in its capacity to persist as a parasite in individuals or communities This persistence has been well demonstrated by ROODYN in a seven-year study of families attending the Woodberry Down Health Centre In 1951–58 ROODYN[1] studied seventeen families in which multiple staphylococcal infections arose In eleven of these families phage-typing showed that the same staphylococcus had spread from person to person in the family In two families a single strain of staphylococcus persisted for over six years In each of these two families 1 member was prone to recurrent lesions, and although both were nasal carriers it was only when they developed sepsis that other members of the family became infected In a second paper ROODYN[2] describes a study of 81 patients who first presented with staphylococcal infection in 1951–52 and were kept under observation for the following seven years In this period 23 of the patients had recurrences, in 14 cases there was only a single recurrence a few weeks after the initial lesion, but 9 of the patients had repeated attacks of boils From a study of the phage type of staphylococcus isolated from successive infections in these 9 patients it was shown that the same organism had persisted for over six years in 2 cases, for four to five years in 5 cases, and for one and a half to three years in 2 cases Identical strains were isolated from the nose and lesion of 16 of the 23 patients who had recurrent infections In 5 of these patients the nasal carriage persisted for more than four years 2 patients were persistent skin carriers without being nasal carriers

To what extent does this situation in the family differ from that in hospital? There, too, staphylococci may persist, and the same strain of staphylococcus may predominate in a hospital community for many years, although the composition of the community is constantly changing[3,4] One obvious difference is the greater severity of the infection in the hospital Patients in hospital are of course peculiarly susceptible to infection, but many would affirm that at any rate some strains of hospital staphylococci not only are more likely to be resistant to antibiotics but also are of enhanced virulence[5–8]

There is, of course, a two-way traffic Many patients —particularly babies—take hospital staphylococci home in their noses and may retain them for many months[9,10] This is reflected in the increasing incidence of penicillin-resistant strains isolated in general practice[11–13] Possibly

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1 Roodyn, L *J Hyg , Camb* 1960, 58, 1
2 Roodyn, L *ibid* p 11
3 Rountree, P M , Barbour, R G H *J Path Bact* 1951, 63, 313
4 Barber, M , Hayhoe, F C J , Whitehead, J E M *Lancet*, 1949, ii, 1120
5 Rountree P M , Freeman, B M *Med J Aust* 1955, ii, 157
6 Beavan, D W , Burry, A F *Lancet*, 1956, ii, 211
7 Shooter, R A , Smith, M A , Griffiths, J D , Brown, M E A, Williams, R E O , Rippon, J E , Jevons, M P *Brit med J* 1958, i, 607
8 Barber, M , Dutton, A A C , Beard, M A , Elmes, P C , Williams, R *Brit med J* Jan 2, 1960, p 11 See *Lancet*, Jan 16, 1960, p 157
9 Ludlam, G B *J Hyg , Camb* 1953, 51, 64
10 Hurst, V *ibid* 1957, 55, 299, 313
11 Roodyn, L *Brit med J* 1954, ii, 1322
12 Roodyn, L *Proc R Soc Med* 1956, 49, 263
13 Gould, J C , Cruikshank, J D *Lancet*, 1957, ii, 1157

strains carried in the nose in the absence of sepsis lose some of their virulence.

Conversely patients and possibly visitors may bring staphylococci with them into hospital. A patient with a staphylococcal lesion, however small should if possible be isolated, but it is doubtful whether anything is gained by treating all nasal carriers on admission. If strains spreading in a hospital are really of enhanced virulence, nasal carriage of a less virulent strain might be a protection. As for visitors, most workers regard these as a negligible source of danger, and, although this view has recently been questioned by Boyd,[14] unless they have boils or other lesions it seems unlikely that they are a serious added menace in a hospital already riddled with staphylococci.[15,16]

The complexity of the subject is again apparent in a new investigation by Bernstein and McDermott[17] from the Bellevue Hospital, New York. They studied the transfer of strains of *Staphylococcus aureus* in the nasopharynx of two groups of patients admitted to a large (40-bedded) medical ward. One group of 130 patients received no antibiotics during their stay in hospital and the second group of 120 patients were treated with tetracycline. On admission both groups had a nasal carrier-rate of approximately 34%. Subsequently the carrier-rate increased by 11% in the first group and by 30% in the group treated with tetracycline. Substitution of one strain of staphylococcus by another took place in 12 of 44 original carriers in the untreated group and 24 of 41 original carriers in the tetracycline group. Thus a new strain of *Staph aureus* was acquired in 29% more of the tetracycline-treated group than among those having no antibacterial treatment. In neither group did the presence of staphylococci in the nasopharynx on admission protect the patient against the acquisition of new strains.

A further point of some interest is that although as might be expected, the tetracycline-treated patients tended to be colonised by drug-resistant strains, this was not so with the untreated patients, who picked up twice as many drug-sensitive as drug-resistant strains (resistant to what drugs was not stated). This finding seems somewhat in conflict with the observation of many investigators, who have shown that nurses, newborn babies, and maternity and other patients, none of whom were on antibiotic treatment, tended to become nasal carriers of drug-resistant staphylococci after a short stay in hospital.[3,4,18,19] Bernstein and McDermott[17] do not mention the source of the "acquired" strains. It would be interesting to know whether they came from other patients or from nurses, and whether the nurses tended to carry drug-resistant staphylococci. In such a large medical ward the influx of new strains may be sufficient to prevent the emergence of a predominant hospital staphylococcus. It is certain that experience in a medical ward, where presumably staphylococcal sepsis was rare, cannot be compared with experience in surgical or maternity wards, where staphylococcal infection is relatively common.

Not too Big

EQUIPMENT is more easily replaced than buildings, and many clinical departments working in dingy and inconvenient surroundings are nevertheless able to offer their patients the latest forms of treatment. To the mental hospital outdated and ugly buildings are a much heavier handicap, because the patient's surroundings are relatively important. Whereas in other specialties equipment has altered with changes in practice, in psychiatry monolithic buildings have often hampered the introduction of new ideas and procedures. That so much has been done, despite the discouragement of bricks and mortar and the influence of asylum baroque, is proof of the strength of these ideas. But progress will become quicker and experiment more hopeful if full advantage is taken of even the present modest opportunities for hospital building. Psychiatric services and architecture is thus a timely choice of subject for the first[1] of a series of occasional papers which the World Health Organisation is to publish to stimulate international thinking and discussion. Of the three authors Dr Baker is medical superintendent of an English mental hospital, Dr Sivadon of a group of French ones, and Mr Llewelyn Davies the director of the Nuffield Foundation's division of architectural studies, and they have combined to offer practical advice and a thoughtful reassessment of principles.

Unfortunately many mental hospitals were built at a time when the pattern of care was custodial. Large hospitals in large grounds were accordingly erected in remote rural areas. But yesterday's advantage is often today's defect. The aim of psychiatry is no longer to guard and soothe the patient, but to help him to return to everyday life. For this the old-fashioned hospital is usually ill suited—forbidding in appearance, inaccessible by public transport, difficult to staff, expensive to maintain. For the vulnerable patient, as Dr Baker and his colleagues point out, there are still more drawbacks. When the patient arrives the pretentious façade of the massive block will tend to make him feel small and frightened. Inside he will find long corridors bewildering in their similarity. In the ward he will find no privacy, but perhaps the stale smell of inadequate sanitary arrangements. The room where he lives will be either large and lofty or a tiny cell, neither will have normal domestic proportions.

The needs of the mental patient vary with the stage of his illness. In the acute phase he requires a small secure area and the reassuring support of one person. As he improves he should be introduced to a small family-sized group, and gradually encouraged to widen the ambit of his activities and contacts until he is sharing in all the life of the hospital in preparation for his return to the community. The amorphous mental hospital, in the past at any rate, was a form of blunderbuss therapy Little attempt was made to match the patient and his setting Dr Baker has described[2] how much can be achieved, even under the stringencies of real life, in an unwieldy hospital if it is broken up into smaller units and communities Offered the freedom of planners, he and his colleagues have drawn up a workmanlike scheme for diverse buildings to offer diverse care

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[14] Boyd A. M *Brit. med J* Feb 20 1960, p 563

[15] Stengold, L., Ashworth, L *ibid* March 19 1960 p 878

[16] Lowbury E. J L. Jackson, D M. *ibid* April 16, 1960 p 1203

[17] Bernstein, C. A. McDermott, W *New Engl J Med* 1960, 262, 637

[18] Barber, M., Wilson, B D R. Rippon, J E., Williams, R. E. O *J Obstet Gynæc. Brit. Emp* 1952, 60, 476

[19] Brodie, J, Sommerville, T, Wilson, S G F *Brit. med J* 1956, i, 667

[1] Baker, A., Llewelyn Davies, R., Sivadon, P Psychiatric Services and Architecture. W.H.O public health paper, no 1 Geneva 1959 Pp 59 2s 6d.

The *outpatient clinic and early-treatment centre* are the basic unit, and need only simple accommodation a waiting area which can be temporarily divided for informal groups, a secretary's office, two treatment rooms, and two consulting-rooms, which should not be so large as to frighten the patient, which yet should look like a consulting-room, but which should not display any alarming apparatus In country districts some might have a small inpatient unit of 6 beds The *day hospital* can be grouped with the outpatient clinic, but should be self-contained It would include more small rooms for treatment and larger rooms for group therapy, occupational therapy, or physiotherapy, a dining-room, and a social club

The *psychiatric hospital* proper should be a "social field" of 300 patients and 12 doctors It should encourage the patient's progress by varying his living conditions At first he will need a small individual room or cubicle, later he will join a small group of 4–8 people and gradually pass to larger groups of up to perhaps 30 Ward units should be divisible into areas suitable for these groups The ward should offer security, reassurance, and some privacy The patient should have some place to keep his own belongings He should himself manage door-closing devices, wash-basins, and water-closets Where security is essential, precautions should be simple and unambiguous, devices which only give an illusion of liberty may make the patient feel that he is being deceived Familiarity enhances security and plans of the hospital should be posted in each ward Prominent clocks, calendars, and timetables of the day's activities will help the patient to reorient himself in time and place

Some patients will need a small workroom inside the ward Small workshops will take patients from several nearby wards Larger more distant workshops will draw patients from the whole hospital A central part of the hospital would offer opportunity for communal life—a restaurant, little shops, the hairdresser, library, lecture-room, chapel The medical services would also have a centre, which should be in a separate building apart from the wards and the social centre Special units are proposed for special groups, such as mothers and babies, children, and old people

For many patients an *aftercare home* will be the first step towards rejoining the community It should be independent of the hospital, should be small, and should look similar to other houses in the town For this purpose conversion has some advantage over new building For the long-stay schizophrenic a *working settlement* of 20–50 patients is proposed

These therapeutic principles impose principles of design Buildings must provide a gradation of spaces and flexibility in their arrangements They should suggest a semidomestic environment, such as a residential college, where a sense of purpose is explicit. The wards should be regarded as living quarters for patients and other services should be housed in separate buildings grouped imaginatively over the site in a variety which will help to reeducate the patient in his grasp of space But the overriding principle that emerges is the need for modesty in size As the authors put it, "many cultures will feel the need to provide large and imposing buildings to show their prowess and ability Such building could house research institutions, library facilities, and congress halls, but they should not be used for hospitals"

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[2] Baker, A *Lancet*, 1958, ii, 254

Annotations

GUT

In 1937 the late Sir Arthur Hurst formed a small club of thirty-six colleagues interested in gastroenterology This group became the nucleus of the British Society of Gastroenterology, which has prospered with the development of the specialty As the size and authority of the society grew, so did the need for a British journal devoted to the subject In 1958 the society resolved that a quarterly journal be prepared, and the first issue has appeared lately

Entitled with unelaborate brevity *Gut*,[1] the journal is edited by Mr Harold Edwards and Dr F Avery Jones, with a committee of other experts In a foreword, Mr Edwards stresses the integration of all types of general medical and surgical knowledge which is required to resolve gastroenterological problems The first issue, with its varied contents, is promising

In an account of blood-group distribution in peptic ulcer and gastric cancer, Doll et al[2] emphasise the susceptibility of patients of blood-group O to stomal ulceration, but they have failed to confirm previous observations that antral gastric ulcers and neoplasm are especially liable to develop in subjects of blood-group A

From two necropsy surveys covering some 20,000 examinations—one retrospective from Leeds and the other prospective from various parts of the country—Watkinson[3] concludes that ulcer frequency in the general population is best estimated by studying the prevalence of ulcer in patients who have died from causes other than ulcer

The increasing recognition of the relation of hormonal secretion to gastrointestinal diseases is reflected in several articles One describes the effect of corticotrophin, cortisone, prednisone, and aldosterone on secretion from denervated gastric pouches in dogs[4] All these agents, given in pharmacological doses, increased the volume of acid in the gastric secretions and reduced the content of pepsin, sodium, and potassium The augmentation of secretion, which developed after three to five days, was apparently produced by an increase in the number of parietal cells and a reduction in the number of cells secreting pepsin The concept that serotonin might play a major part in determining the rhythm of bowel movement in man was tested, with negative results, by demonstrating that the urinary output of 5-hydroxyindole acetic acid was not increased in various types of diarrhœa and that, although a banana diet produced a five-to-ten fold increase in serotonin excretion in healthy subjects, diarrhœa was never induced[5]

In a history of the British Society of Gastroenterology

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[1] *Gut*, March, 1960 Articles may be sent to the Editorial Secretary, *Gut*, Central Middlesex Hospital, Park Royal, London, N W 10 Subscriptions (£3 per annum, single number 17*s* 6*d*) may be sent to the Publishing Manager, British Medical Association, B M A House, Tavistock Square, London, W C 1

[2] Doll, R, Swynnerton, B F, Newell, A C *Gut*, 1960, 1, 31

[3] Watkinson G *ibid* p 14

[4] Clarke, S D, Neill, D W, Welbourn, R B *ibid* p 36

[5] Connell, A M, Rowlands, E M, Wilcox, P B *ibid* p 44

Dr Thomas Hunt[6] says that publication of the new journal is justified both by the special interests of this specialty and by the size and authority of the society The first issue helps to vindicate his claim

PROPHYLAXIS OF RHEUMATIC FEVER

NOWADAYS most physicians dealing with rheumatic fever, especially in children, pay much attention to prophylaxis against streptococcal respiratory infections This measure, applied continuously during the years of greatest susceptibility to recurrence after an attack, provides a high degree of protection against further cardiac damage. Much of the work on prophylaxis has been done in the U S.A., where a high recurrence-rate in unprotected cases seems to be the rule[7] In the United Kingdom recurrence-rates, though rather poorly documented, are apparently lower, but evidence has been forthcoming that here too prophylaxis is worth while,[8] and efforts have been made to overcome objections to it[9] One of the main difficulties is in securing regular administration continuous prophylaxis with oral penicillin or sulphonamide depends on a close understanding between family doctor, parents, and children The difficulty of making sure that patients continue to take their tablets increases as the interval since their last rheumatic attack lengthens, and when recurrences do occur it is equally difficult to establish whether prophylaxis has in fact been omitted Daily prophylaxis is usually regarded as more efficacious than administration of penicillin only for treatment of respiratory infections —although this method, properly and consistently used, can undoubtedly protect against recurrence[10]

Lim and Wilson[11] in New York studied ambulatory rheumatic children attending a rheumatic clinic monthly for six years One group of patients (group 1) received continuous oral penicillin prophylactically and were also treated with penicillin when respiratory infections occurred. Another group (group 2) received penicillin only for treatment of respiratory infections In each group, treatment consisted of a full ten-day course of an oral preparation, started at the onset of symptoms β-hæmolytic streptococci were isolated from the two groups with about the same frequency (the organisms were apparently not serologically grouped) and the incidence of upper respiratory infections was also similar Likewise the recurrence-rates were not significantly different the recurrence-rates per 1000 patient-months were 7 5 in group 1 and 4 6 in group 2 for cases in which the last attack had been recent, and 3 9 and 2 4 when the interval since the last attack had been longer In two British series,[8 12] in which prophylaxis had been continuous, there was a smaller but still significant recurrence-rate (about a quarter of that reported by Lim and Wilson)

It may thus be argued that the risk of recurrence is no greater when penicillin therapy is confined to the treatment of respiratory infections than it is with full prophylaxis But this has been shown to apply only where careful medical supervision minimises the hazard of infections remaining untreated Continuous prophylaxis is surely at present the most generally effective protective measure against recurrences

MIGRAINE

MIGRAINE may be viewed narrowly as an episodic headache with features suggesting a vascular origin, or as a syndrome with more widespread bodily disturbances What initiates either the vascular change in cranial arteries or the visceral dysfunction? Careful clinical studies can still be useful here, and Selby and Lance[1] have reviewed five hundred cases confirming many previous observations, some of which are well known

In almost a quarter of their cases symptoms started before the age of 10 years In 15% there was a family history of epilepsy, and in 38% one of allergy 67% regarded emotional upsets as a clear precipitating factor 18% had clouding or complete loss of consciousness during attacks Such disturbances of consciousness, which usually are not apparently epileptic, may occur only for a limited time—perhaps during adolescence or at the menopause In treatment the value of ergotamine tartrate was confirmed Histamine as an intravenous infusion (not administered for slow graded " desensitisation ") also proved valuable, though Selby and Lance wonder whether this acted primarily on soma or on psyche

In considering the migraine syndrome we may be misled by too exclusive attention to the headache Gastrointestinal disturbances and peripheral vasomotor symptoms occur, and abnormalities of fluid balance are not uncommon These may be secondary to disturbances of neural control, but possibly the imbalance, the electrolyte changes which accompany it, or some associated endocrine abnormality plays a primary part in the attack.

PHÆOCHROMOCYTOMA OF THE URINARY BLADDER

PHÆOCHROMOCYTOMAS (chromaffin paragangliomas) may arise in any part of the scattered extra-adrenal chromaffin-tissue system, which is situated in the prevertebral tissues of the abdomen as well as in the adrenal gland itself Mac Keith[2] collected 165 reported cases, of which 152 were of adrenal origin and 13 arose in the retroperitoneal tissues between the kidneys The tumours, which are usually benign, may cause paroxysmal hypertension or the adrenal sympathetic syndrome, leading to death if the tumour is not removed, or they may have no hormonal effects

Pugh et al[3] have described 4 cases of phæochromocytoma of the urinary bladder, only 3 other such cases have been reported previously[4–6] These 7 cases are of great clinical and pathological interest All the patients were females, whereas adrenal phæochromocytomas occur with about equal frequency in the two sexes The ages ranged from 16 to 74 years, though in at least 3 cases symptoms had remained undetected or latent for many years before the diagnosis was established

The presenting symptoms may be due to the presence of a tumour in the bladder, or may be due to hormonal activity 5 cases presented with hæmaturia, 6 with hypertension (paroxysmal in 2), and 3 with headache, tachycardia, or facial flushing, and in 1 case distension of the bladder with 100 ml of water caused headache and a rise of blood-pressure Operation usually caused a sudden

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[6] Hunt, T *ibid* p 3

[7] Stollerman, G H *Amer J Med* 1954, 17, 757

[8] Bywaters, E G L., Thomas, G T *Brit med J* 1958, ii, 350

[9] Bywaters, E G L, Hallidie-Smith, K *ibid* i, 1234

[10] Catanzaro, F J, Stetson, C A, Morris, A J, Chamovitz, R, Rammelkamp, C H, Stolzen B L., Perry W D *Amer J Med* 1954, 17, 749

[11] Lim, W N, Wilson, M. G *New Engl J Med* 1960, 262, 321

[12] Sanderson, G, St Hill, C A., Chamberlain, E N *Brit med J* March 26, 1960, p 913

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[1] Selby, G, Lance, J W *J Neurol Neurosurg Psychiat* 1960, 23, 23

[2] Mac Keith, R *Brit Heart J* 1944, 6, 1

[3] Pugh, R C B, Gresham, G A, Mullaney, J *J Path Bact* 1960, 79, 89

[4] Zimmerman, I J, Biron, R E, MacMahon, H E *New Engl J Med* 1953, 249, 25

[5] Rosenberg, L M *ibid* 1957 257, 1212

[6] Farley, S E, Smith, C L *J Urol* 1959, 81, 130

fall in blood-pressure The symptoms regressed after removal of the tumours, except in 1 case where the blood-pressure rose 5 patients are still alive 1 died forty months after operation from a cerebral hæmorrhage, and 1 immediately after operation in circulatory failure owing to the hormonal effects of manipulating the tumour

The tumours were found in all parts of the bladder, and their size and weight varied considerably A striking feature of the gross specimens was the alteration in colour during fixation in formol-saline, accompanied sometimes by yellow-brown discoloration of the fixative itself Pigmentation of this type is well known in adrenal phæochromocytomas, and is thought to be due to the formation of an adrenochrome from the adrenaline precursors in the tumour The chromaffin reaction was elicited in only 2 cases, but this reaction is capricious and requires special and rapid fixation An excess of noradrenaline was demonstrated in the tissue of 2 of the tumours 6 were benign, and 1 was malignant with metastases Metastases are the only reliable criterion of malignancy, because the tumour cells lie in the muscle coat of the bladder wall and even grow into the perivesical tissues, thus simulating infiltrative growth Such an anatomical distribution supports the belief that the tumours arise from paraganglia related to the autonomic nerves of the bladder wall

The analysis of these 7 cases suggests that diagnosis before operation should be possible in some two-thirds of the cases Hæmaturia combined with the adrenal sympathetic syndrome is almost pathognomonic Hæmaturia with hypertension, especially if paroxysmal, is suggestive The effects of adrenergic-blocking agents, the estimation of the urinary catechol amines, and bioassay of the excised tumour will substantiate the diagnosis in most cases Rosenberg draws attention to two features of vesical cases First, the excretion of urinary catechol amines may not return to normal until about a month after the tumour has been removed, and a temporarily raised level in the immediate postoperative period should not be regarded as evidence of a second tumour or of metastatic spread (nevertheless, in the case of Farley and Smith[6] a polypoid tumour obscured the right ureteric orifice and at operation a second nodule of tumour tissue was found at the bifurcation of the hypogastric vessels) Secondly, Rosenberg induced a hypertensive attack in his patient by distending the bladder with fluid introduced through a urethral catheter

ROGER BACON AND THE PHYSICIANS

WE do not know for certain the time or place of Roger Bacon's birth, or when he died, but probably he was born in Somerset, about 1214, and lived till he was over eighty He is reputedly buried in Oxford, and it was in that city that he is likely to have carried out his most notable scientific investigations That he invented spectacles, left the earliest recorded formula for gunpowder, and predicted the development of the aeroplane, are matters of fact The myths which surrounded him even in his lifetime credited him with the creation of a brazen head which talked, and his contemporaries held him to be a necromancer All these things apart, he was certainly a man of unusual scholastic attainments and was accomplished in Greek and Latin, Hebrew and Aramaic It was not, however, his prowess in physics or chemistry, nor the prophetic gifts which enabled him to foresee, for instance, the steam-engine and the telescope, but Bacon's criticisms of the medical profession that Sir John Charles made the subject of his Gideon DeLaune lecture, delivered on April 20 before the Worshipful Society of Apothecaries

There are, he pointed out, at least eight Baconian treatises associated with medicine Four are concerned with the related questions of the preservation of youth, the retardation of old age, and the prolongation of life. Three more are mainly pharmaceutical treatises, and the eighth is the racy and—despite its title—the helpfully analytical book, On the Mistakes of Physicians All are written in simple, easily flowing Latin, and abound in vivid phrases (*Mundo senescente senescunt homines*, ageing men in an ageing world Bacon regarded old age as beginning when the prime of life was over, at about forty-five or fifty, and, like Shakespeare, he recognised phases in the period of declination, and speaks of three groups—the old, the elders, and the decrepit) None of the others can approach the *De Erroribus* in originality of thought, or pertinence of expression But it is the production, as they all are, " of a man of singularly practical mind, who was not in practice and had few opportunities of getting certitude by experience " and it is based upon Galen's system of medicine, as modified by Avicenna and the Arabic physicians, and accepted without question. There is, then, little in the work which can be regarded, even remotely, as clinical There are none of those bedside vignettes we find in the ancient writers, brief and sharply drawn in the case of Hippocrates, copious and discursive when Galen is in charge of the patient Nor is it merely an indictment of, or a diatribe against, contemporary practitioners Its significance lies in its constructive criticism of the system, then prevailing, of what we would now call Medical Education

Bacon listed six principal impediments to those who studied medicine Certain of them, Sir John remarked, are as relevant today as they were in the 13th century The first was an ignorance of language, which denied to many readers the original text of their source books A second was an ignorance among doctors of the drugs they used they could not recognise them, accepted old preparations in place of newly compounded ones, and were put off with substitute or sophisticated remedies Above all, they did not know what they cost Another obstacle to progress was the time wasted in futile arguments, and in the discussion of ill-defined problems, to the neglect of practical study Bacon's next complaint reflects his enthusiasm for astrology, and he held that through failure to enlist its assistance a physician would become unduly dependent on chance and good fortune. Neglect of another subject, alchemy, was the theme of the fifth protest, and the term alchemy included not only the infant science of chemistry but also the whole of botany and zoology Finally, Bacon considered a number of real defects in our knowledge, detailing in particular a lack of precision in diagnosing disease and in classifying it, our ignorance of a specific cure for many conditions, and our inability to explain their causation All these gaps, he argued, might be made good by investigation using experimental methods And, though Bacon was, throughout his life, an important and influential advocate of such methods, nowhere else has he expressed himself more clearly than in the pregnant final sentence of *De Erroribus* " Neither the voice of authority, nor the weight of reason and argument are as significant as experiment, for thence comes quiet to the mind "

Special Articles

HOLIDAY ADMISSIONS TO A GERIATRIC UNIT

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FROM time to time the geriatric service in the north of Glasgow is asked to admit chronic invalids to hospital temporarily so as to allow their relatives to go away on holiday Most of these requests come from relatives who are successfully looking after an elderly person not in need of permanent hospital care. Other patients really need hospital care, and the relatives have reached a point where they cannot carry on without a rest, though they ask to have the patient back home again after their holiday

The temporary admission of both groups of patients can greatly help the relatives, and can also offer the unit an opportunity for useful work. But while many patients benefit considerably from their stay in hospital, others react adversely to the change of environment During the past year 46 patients were admitted as " holiday cases " to geriatric units in the north of Glasgow, and we describe here the conditions in which they were cared for at home and the benefits and hazards of their hospital admission

THE PATIENTS

Of the 46 patients, 19 were men and 27 were women

6 were under the age of sixty, of whom 4 had disseminated sclerosis 14 were between eighty-one and ninety, and 3, all women, were over ninety The average age of the men was sixty-nine and of the women eighty Cerebrovascular degeneration and cardiovascular degeneration were the major diagnoses in half of the cases, and a third had other chronic neurological disorders, such as hemiplegia and parkinsonism. The other patients had as their major diagnosis arthritis, osteoporosis, carcinoma, and amputation of a leg or legs Many patients had multiple degenerative disorders 18 were incontinent of urine at home, and 14 were incontinent of fæces

21 patients had not been treated in hospital for their present ailments Few had been investigated or were receiving specific treatment We investigated all patients when they came in for their holiday and established a diagnosis For a third of the patients it was different from, or additional to, the diagnosis given before admission Most of the patients were treated with drugs, and 20 also received physiotherapy, 10 occupational therapy, and 11 were supplied with appliances, such as walking-aids, hearing-aids, commodes, a rubber urine-bag, and a hernia belt. Several wheelchairs and callipers lying at home unused, or incorrectly used, were brought to hospital with the patient and were suitably modified By these means we succeeded in improving the general health, the ambulation, and independence of 17 of the patients, who returned home happy with their stay and appreciably easier for their relatives to look after The following case-history is typical of this group

A man of 67 had been confined to bed for three years with a diagnosis of cancer of the kidney and diffuse secondaries in the testes and the brain. He was dull, demanding, and unwilling to help himself, and his wife was exhausted by caring for him. He appeared physically robust, had full movement of all limbs, and no neurological abnormality One kidney had been removed for cancer five years ago, and two years later one testis was excised, but showed only chronic inflammatory changes Our investigations revealed excellent function of the remaining kidney and no evidence of secondaries At first the patient resented attempts at reassurance and rehabilitation, but when he left hospital three months later he was able to get out of bed unaided, wash himself, dress himself, feed himself, walk to the lavatory and climb one flight of stairs, much to his own satisfaction and to the indescribable relief of his wife

Many other patients, however, needed little or no rehabilitation, or were unable to benefit from it. 15 of these spent a more or less uneventful time in hospital and returned home unchanged Most of them found their hospital stay a pleasant enough interlude and said they would be happy to return another time.

Among the others were many whose stay was unfortunately complicated by intercurrent illnesses or accidents, or who deteriorated physically or mentally while in hospital.

Several patients contracted infections of the chest or urinary tract. Many were bewildered by their change of environment and became confused and agitated. Others grieved for absent relatives or felt rejected by them and became depressed. Some patients became incontinent of urine for the first time, and a few developed pressure-sores, notably one man of sixty-four with disseminated sclerosis His wife had nursed him for seventeen years without a single break occurring in the skin, but he developed a sacral sore two days after his admission, which took several weeks to heal A woman of sixty-nine fell and fractured the neck of her femur She became bedfast and could not return home.

4 patients died during their stay in hospital, 2 died immediately after returning home, and 10 others were sent home appreciably worse than when they came in

A woman of eighty-nine with parkinsonism, depression, and urinary incontinence became more incontinent and depressed in hospital, developed pressure-sores, and died five weeks after admission.

A man of sixty-four with right hemiplegia, aphasia, and amputation of both legs died one week after admission from coronary artery occlusion.

A man of seventy-six was severely demented, aggressive, and incontinent on admission, and the relatives were advised not to attempt to take him home again after their holiday He was transferred to a long-stay ward where he died of pneumonia ten weeks after admission.

A woman of eighty-six had shown signs of progressive dementia for four years She was aggressive and very confused in hospital, developed incontinence, pressure-sores, and terminal respiratory infection. She died ten weeks after admission.

A woman of ninety-three had been in bed at home for three years following a fall. She was unhappy in the ward and resented attempts at rehabilitation. She remained otherwise well in hospital for three weeks but died on the day after her return home.

A man of eighty-three who was confused and incontinent but ambulant at home became depressed and increasingly confused during a stay of one week in hospital. A small pressure-sore developed but began to heal He died suddenly one week after returning home

Of the 46 patients, 12 never returned home. 2 of these were placed in an eventide home as their relatives were no longer able to look after them 6 were transferred to long-stay accommodation—1 to a mental hospital—and 4 died in hospital Only 26 of the remaining 34 were sent back home as planned within one month, the rest remaining in hospital for up to three months Sometimes the stay was prolonged because the patient was still learning to walk, or was in some other way continuing to benefit from active treatment. More often the delay was because the patient was being nursed over a complicating illness, or because illness among the relatives prevented them from taking the patient back home Several times we discouraged the return home of a patient when we were convinced that the nursing burden was too heavy for the relatives and could not be sustained

In general the patients who fared worst were the very elderly, confused, and incontinent 1 patient in 5 under the age of seventy-four deteriorated or died, against 1 in 3 over that age The results were apparently better among the men than the women, but this was merely due to the higher proportion of younger patients among the men

In assessing the results it must be remembered that many of these patients were going downhill at home, and some would have deteriorated or died even if they had not been admitted to hospital Nevertheless we have little doubt that removal to hospital for these patients is attended by very real risks

THE HOUSEHOLD

We visited all the patients at home both before and after their stay in hospital, and we interviewed the relatives caring for them The needs of the invalids dominated the lives of these people When we asked what they thought of the patients' temporary move to hospital we often received the answer " It was a godsend " For 8 of them this was their first holiday in over five years, and fewer than half of them had had a break during the previous two years Although a few were anxious about the elderly person left behind, almost all had immensely appreciated their holiday

11 of the patients had been cared for at home for more than ten years and 17 for between five and ten years 13 patients were wholly confined to bed, and 8 others were only able to sit up in a chair for an hour or two each day A third of the patients had not been out of the house for more than five years Only 16 of them could go to the lavatory by themselves, 11 needed help whenever they had to go, and the remaining 19 had to use a bedpan or commode

Most of the homes were rather better than those of the ordinary admissions to our units All but 7 of the families lived in houses of three or more apartments On average there was one person to a room and three and a third people to a household On the other hand no fewer than 18 of the households lacked bathrooms, 15 had no running hot water, and 7 of these patients were being cared for in houses with no inside lavatory

THE RELATIVES

The relatives looking after these patients were mostly middle-aged women

12 wives were looking after their husbands, but we had no cases of husbands caring for wives 6 patients were looked after by their sister 22 daughters were caring for parents, but no daughters-in-law 1 son was looking after his father, and incidentally sacrificing his chance of marriage by doing so 3 nieces and 1 family friend were looking after an old person because there was no-one else to do it, and they did not want the patient to end his days in an institution 1 old person had a paid housekeeper doing the work

The average age of these relatives was fifty-six None was under thirty, 6 were between seventy and eighty years of age, and one woman of ninety-one was being looked after by her sister of eighty-two Only 11 of these 46 people said they were in good health The others were having medical attention for different ailments or for symptoms of physical and mental strain—notably fatigue, back strain, and nervousness

What is it like to look after an ill old person at home? We restricted our questions to the care of the patients' excretory functions, the care of the skin, and the problem of leisure

A third of the patients could go to the lavatory alone, and a quarter could go with help, but 19 could not go to the lavatory In less than half the households were commodes, bedpans, and urinals used 18 patients were incontinent of urine and 14 were incontinent of fæces The common method of dealing with incontinence in bedfast patients was to tear up old sheets for draw-sheets and for wrapping between the patients' legs These were washed and used again rather than destroyed. One or two ambulant incontinent patients spent their second childhood, like their first, wrapped in squares of turkish towelling

We were impressed by how much more could have been done to help their relatives by advice on disposable incontinence pads (which we found in use in only one household), by greater provision of commodes, urinals, rubber sheets, and rubber urine-bags, all of which are readily available, and by the provision of a foul-laundry service

As it was, a tremendous amount of extra laundering, often of the most unpleasant sort, fell to the relatives They all insisted on washing the patients' soiled linen by hand themselves, and would not allow anyone else to handle it For the incontinent patients there was a washing to be done at least once and sometimes twice a day, and some of the houses had no running hot water A quarter of the households had washing machines, a quarter used a laundry, launderette, or public wash-house In the others all the washing was done by hand—sometimes as many as 70 pieces a week

The care of the skin was almost always done by washing the part, drying, powdering, and rubbing with spirit, petroleum jelly, or zinc and castor-oil cream Only half of the families were helped by the district nurse, who gave a bed-bath once or, occasionally, two or three times a week, and who then attended to the skin It is a tribute to the care of these relatives that only two patients had pressure-sores when admitted to hospital

Many patients were confused and disoriented, liable to get out of bed and fall, to turn on the gas, or to endanger themselves in other ways, and this was a problem to the housewife who was afraid to leave the patient alone when she went out for shopping or leisure Neighbours, friends, and other members of the family were sometimes able to help The person looking after the patient usually managed to go out on only one evening a week A quarter of them said that they never went out at all

Only one family had a local-authority home-help, and two others had private domestic help We concluded that the home-help service could do little to help these households, for the problem was seldom one of home management, but rather of nursing care

The following cases illustrate the burden of care borne by relatives

Two unmarried sisters looked after their mother of seventy-four who had been confined to bed for four-and-a-half years with multiple cerebral thrombosis and blindness She was doubly incontinent and was nursed in skirts made out of flannelette and washed by hand daily The daughters regretted allowing their mother going to hospital because she was unhappy there, and gave up their holiday to take her home There she developed gangrene of both feet, but the daughters continued looking after her

A woman of eighty-eight, blind, arthritic, and doubly incontinent, was looked after during the day by a married daughter who lived nearby, and at night by a second married daughter who had come every evening for eleven years to sleep in her mother's house

DISCUSSION

This study illuminates one corner of the large problem of home care of elderly invalids We saw only the minority of patients whose relatives sought holiday relief Many households in this group were labouring under difficulties that could have been eased by the fuller use of available facilities, which had been perhaps insufficiently made known to them A possible solution might be an advisory service for relatives caring for the elderly at home, based on a consultative health-centre for the elderly

Our principal task was to assess the value of temporary holiday admission, and here our impression is that this service is so necessary and so beneficial to the relatives that it should be provided by geriatric units Such a service makes economic sense, for it helps the relatives to keep the patients out of hospital for eleven months of the year But because of the attendant risks we make the following recommendations

1 At the request of the general practitioner all patients should be visited in their own homes by the physician from the local geriatric unit some weeks before the proposed holiday After assessing the circumstances he should advise the relatives on the probable outcome and, usually, should leave to them the decision whether or not to proceed with the arrangement. He should emphasise the poor prognosis in the very old and confused, and should mention that there is a definite mortality associated with the move

2. In planning the patient's transfer to hospital the physician should be generous with time. It is best for the patient to be taken to hospital a week before the relatives go away This enables them to make their holiday arrangements free from anxiety, and allows them to visit the patient in hospital before going away They can also satisfy themselves that he has been left in good hands and is not grieving for them. In the same way the relatives should be allowed a week to settle down at home again before the patient returns From the patient's point of view a very short stay in hospital causes disorganisation without achieving any real benefit and we think a stay of four weeks is suitable.

3 The physician should decide in advance the kind of ward suitable for the patient. If he thinks the patient needs investigation and rehabilitation, he will reserve a bed in his acute unit. But the elderly bedfast and confused patients will be better off in the quieter atmosphere of a long-stay ward. Some of our failures may have been caused by exposing unsuitable patients to the brisk activity of a rehabilitation unit because of shortage of beds in long-stay wards

4. Some of the distress caused to patients by hospital admission could have been avoided by giving them more privacy Many elderly patients, after being confined at home for a long time, are upset by contact with other old people, especially when some of these are harrowing cases of confusion and incontinence. This attitude was expressed to us by many relatives in such words as, "We quite understand that hospitals have to put everyone in together, but Mother is very easily upset by seeing other people suffering Wouldn't it be possible for her to have a little privacy? We would be willing to pay for it." One cannot but sympathise with these people. The alternative is to send the patient to a nursing-home, but the cost is often prohibitive, and nursing-homes cannot provide facilities for investigation and rehabilitation, while they are often unprepared to accept some patients—e.g., the incontinent. There are no amenity beds in our geriatric service, but we believe that there is a demand for such beds

We have stressed the dangers of temporary admission of old people to hospital, because these are perhaps insufficiently appreciated. But our own most vivid impression of the work has been our pleasure in giving most of these overworked households a period of real relief from their burden. We have had the additional satisfaction of making many bedfast patients ambulant once again and putting them on the path to independence. We feel that a service which has these benefits to offer should be made widely available to those who need it.

We wish to thank our colleagues Dr J C. Crone, Dr Aloysius Dunn, Dr Nanette Nisbet and Dr A. M. P Thomson, under whose care many of these patients were admitted. We also thank Dr W F Anderson for his advice and encouragement.

Symposium

GENETIC STUDIES IN GASTROENTEROLOGY

A SYMPOSIUM on the genetic approach to the study of gastrointestinal disease was held by the Gastroenterology Research Group on March 31 in New Orleans under the chairmanship of Dr VICTOR A. MCKUSICK (Baltimore)

Dr MCKUSICK said that analysis of genetic factors in the disorders of a given system showed that the disease-entities tended to fall into two classes rarer conditions in which the genetic factor was relatively straightforward, and common disorders in which genetic and environmental factors collaborated and made the genetic analysis more complicated The questions asked and the approaches to the answers tended to be different in the two categories In the rarer disorders interest centred on the nature of the basic biochemical defect and on the formal genetics (precise mode of inheritance, gene frequency, mutation-rate, relative fertility) In the commoner disorders, the questions were was there a significant genetic factor in the pathogenesis. and by what mechanism did genes determine susceptibility to the disorder? The purpose of the symposium was to illustrate methods rather than to cover exhaustively genetic factors in alimentary disease

Hereditary Hyperbilirubinæmias

Dr BARTON CHILDS (Baltimore) contrasted the clinical and chemical features of four types of hereditary hyperbilirubinæmia the Dubin-Johnson syndrome (D-J), the Rotor syndrome (R), the Gilbert syndrome (G), and Crigler-Najjar (C.-N.) syndrome Taking all cases of D-J in the literature, the sex-ratio was 4 36 males to 1 female. If the cases reported from military installations were excluded the ratio became 3 12 males to 1 female. But when the sex of affected sibs of patients was considered, the male-female ratio was nearly 1 1, though still slightly greater than 1 Parent-to-child transmission was observed and either parent seemingly may transmit the trait, although the numbers were small. In R, parent-child transmission also occurred, suggesting dominant inheritance. In G, a defect in glucuronide conjugation of bilirubin could be demonstrated in those individuals with higher serum-bilirubin, but not usually in those with levels of bilirubin less than 5 mg per 100 ml C.-N. was clearly inherited as an autosomal recessive. The relation between G and C.-N. might have any one of three bases (1) the same gene in heterozygous and homozygous state, respectively, (2) different genes at difficult loci controlling different enzymes, and (3) alleles at the same locus

Hæmochromatosis

Prof. MAURICE LAMY (Paris) described a family study of hæmochromatosis in which 3 cases of hæmochromatosis were found among brothers of 30 probands Nearly all patients had a raised serum-iron level and a raised iron-saturation coefficient of siderophilin. Among 67 offspring of probands the means of plasma-iron concentration were essentially the same for males and females under 15 years of age and for females over the age of 15 Sons over the age of 15 showed an elevation of the mean value and appeared to comprise two groups, about half having an abnormality of iron metabolism The experience was considered consistent with the hypothesis that hæmochromatosis was manifest in individuals heterozygous for one gene. Patients with juvenile hæmochromatosis, especially those born of consanguineous matings, may be homozygotes Of 30 patients, 10 could be considered as definitely alcoholic Although alcoholism may hasten clinical decompensation, a more fundamental role was doubtful The recessive hypothesis favoured by some workers was based on little more than the observation of multiple affected sibs and the failure to observe the disease in successive generations Since mothers were likely to transmit the disease without manifesting it, since clinical expression occurred late in life, and since diabetes, heart-failure, and cirrhosis may be otherwise interpreted in the family history, the rarity of reported direct transmission was not surprising Only 2 instances of consanguinity in parents of patients were discovered in the literature

Cystic Fibrosis of the Pancreas

Dr **Arthur G Steinberg** (Cleveland) said that two frequent misconceptions of clinicians were (1) that if truly genetic a disorder would by necessity occur in more than one member in most families studied, and (2) that a recessively inherited trait should occur in precisely 25% of the members of a large group of collected sibships In connection with the first point he indicated that of 2-child families only 6% could be expected to show 2 offspring affected by a recessive trait and not until one reaches families of 7 children can a majority (56%) of them be expected to show more than one affected member In connection with the second point he indicated how mode of ascertainment influenced the proportion of affected sibs observed In 141 cystic-fibrosis sibships studied by Steinberg and his colleagues, 48 9% of offspring were affected Corrected for mode of ascertainment the data were consistent with a recessive hypothesis Steinberg found cystic fibrosis rare in Negroes and suspected that it was totally absent in pure Negroes Two previous estimates of frequency of the disease (q^2) had been 1 in 600 and 1 in 1000 live births, giving a gene frequency (q) of 0 041 or 0 031 respectively To maintain such a high gene frequency in the face of gene loss from death of homozygotes before reproduction, one could suggest either a mutation-rate of 1 in 300 or 1 in 500 genes per generation or a relative fertility advantage of the heterozygous carrier over the homozygous normal, estimated by q/p, or about 3% That is, for each 97 offspring of a homozygous normal parent there should be 100 offspring of a heterozygous parent In an intensive survey in Ohio Steinberg attempted total ascertainment of cases of cystic fibrosis among births between 1950 and 1953 Thereby, he arrived at an estimate of 1 in 2800 live births for frequency of the disease, 0 019 for gene frequency and 1 in 27 for frequency of heterozygotes A fertility advantage of less than 2% would alone maintain the gene frequency An impracticably large sample would be required to demonstrate such advantage Cystic fibrosis was the most frequent genetically determined lethal disease of childhood

Intestinal Polyposis

Dr **T Edward Reed** (Ann Arbor) said there may be five different genetic varieties of intestinal polyposis (1) classical familial polyposis of the colon, which in Michigan appeared to have a frequency of about 1 in 8000, (2) the Peutz-Jeghers syndrome (generalised intestinal polyposis with melanin spots of the oral mucosa, lips, and digits), (3) the Gardner syndrome (colonic polyposis associated with osseous and soft-tissue tumours), (4) the possible syndrome of Turcot-Després-St Pierre (colonic polyposis and brain tumour), and (5) possibly single isolated polyps arising in families The inheritance of the first three and the fifth was dominant It was uncertain what the relationship was between Gardner's syndrome and classical polyposis A large study in Michigan gave the following data in classical colonic polyposis

studied	*No of cases providing information*	*Age of occurrence of feature studied*	
		Mean age (yr)	*Range (yr)*
complaints	32	28 0	5–57
of polyposis	66	30 2	5–58
of cancer	41	35 6	9–60
cancer	29	38 9	9–70

fertility of persons carrying the gene was estimated at 0 78 The indirect estimate of mutation-rate was 2 per 100,000 genes per generation A possible linkage with the MN blood-groups had been described Confirmation would be of theoretical and possible practical interest and might help to settle the question of the relationship of Gardner's syndrome to classical familial polyposis of the colon

Hypertrophic Pyloric Stenosis of Infancy

Prof **Brian MacMahon** (Boston) reviewed familial aggregation in pyloric stenosis and suggested that an environmental influence might more adequately account for all observations than would be a genetic hypothesis Specifically, he incriminated some feature of maternal handling Earlier work had indicated in addition to increased occurrence in siblings of probands an impressive frequency in cousins—a finding not surprising for a *common disorder* (about 3 per 1000) such as this Increased parental consanguinity, previously claimed, was doubtful and in such a common condition was not essential to a recessive genetic hypothesis Some peculiar features of the familial aggregation were (1) incidence was as high in half-sibs as in full sibs, (2) in affected parent-child combinations the mother was the affected parent more often than the father despite the preponderance of males in full series, (3) given an affected parent and child the risk to another child was 40%, (4) father-to-son transmission excluded sex-linked inheritance. In reports collected from the literature, monozygotic twins showed greater concordance than did dizygotic twins, but when a randomly selected series of twin births was investigated no difference in concordance could be demonstrated Suggesting a postnatal origin consistent with environmental causation were the following points

(1) The size of the tumour was related to the age of the infant at operation

(2) In cases of two operations at brief intervals rapid growth of the tumour by the time of the second has been demonstrated

(3) Association with birth-order suggested an environmental influence The association with birth order was greater the older the patient at *onset of symptoms* No *association was demonstrable* in cases with onset in the first weeks of life

(4) Pyloric stenosis was about half as frequent in prematures as in full-term infants

(5) The age of onset was earlier in infants born at home than tho born in hospital

(6) Onset was earlier in infants fed every three hours than in tho fed four-hourly

Duodenal Ulcer

Dr **D A P Evans** (Liverpool) said that research duodenal ulcer illustrated the way in which a genetic approa could contribute to the study of a common condition whi seemed to be due to the interaction of hereditary an environmental influences

Peptic ulcers had been shown to be twice as frequent amon the living siblings of ulcer patients as in the general populatio The relatives of duodenal-ulcer patients tended to have duo denal ulcers, whereas the relatives of gastric-ulcer patien tended to have gastric ulcers

Specific genetic characters contributing to the inherite diathesis had recently been found Series of duodenal ulc patients had more persons of blood-group O and more who wer salivary ABH non-secretors, than did control series Thes associations may be either causal or due to "stratification within the population The latter explanation seeme unlikely because the group-O association had been found many different countries where the basic blood-group dis tributions were different An experimental approach—namely to find whether the associations held within sibships—ha given as yet rather inconclusive results because insufficien sibships had been collected The results did not suggest tha the associations were absent within sibships

Since there was a distinct possibility that these genet characters were causal, certain physiological information wa reviewed There was a possibility that healthy group-O person tend to produce more hydrochloric acid in the stomach tha persons of group A In this connection it was interesting to note that stomal ulcer was even more closely associated with group O than duodenal ulcer What evidence there was tended to suggest that quantitative factors in blood-group substance concentrations in body liquids were not responsible for the different susceptibilities of different phenotypes to duodenal ulcer

From the biological point of view duodenal ulcer represented the selective effect of environment on a presumably balanced polymorphic system of eight phenotypes By viewing ulcer in this way and studying the environmental influences acting on phenotypes of different susceptibilities, with and without ulcer, a clue may be obtained to the factors in the environment which cause duodenal ulcer

Public Health

Foaming Waters

A NEW report[1] by the Standing Technical Committee on Synthetic Detergents, published last week, says that while there has been little change in the consumption of powdered detergents during the past two years the domestic use of liquid detergents has increased, and that foaming on rivers and canals and at sewage works continues to give rise to difficulties and complaints

Detergent manufacturers agreed to supply the area of Luton and Harpenden with detergents based on an alternative alkyl benzene sulphonate from Aug 1, 1958 From June that year, regular tests were carried out on sewage and effluent, and a continuing photographic record was kept of foam on the nearby river Lee Unfortunately, it was not possible to replace more than about 70% of the synthetic detergent used in the area with detergents based on the new material The experiment nevertheless shows that a greater proportion of the new than of the old material is removed during sewage treatment, and there has been less foam on the rivers The report adds

> "The Luton experiment has confirmed that the new material is more completely oxidisable than the old Part of the new material is destroyed quickly but a proportion of the remainder seems to be decomposed only slowly, and with some difficulty, so that even at Luton, where an effluent of exceptionally good quality is produced, sometimes at least a proportion of the new material leaves the works It is reasonable to expect that where treatment is less complete than at Luton, removal of the new material is also likely to be less complete Nevertheless, our tentative view is that the replacement of the old material by the new throughout the country would substantially diminish the troubles which have been caused by the increased use of synthetic detergents but it is as yet uncertain whether it will provide as complete an answer as we could have wished Further research by the manufacturers is continuing, but meanwhile the general adoption of the new material in preference to the old would undoubtedly bring about an improvement"

World Health Statistics

The ninth annual statistical report[2] published by the World Health Organisation sets out the demographic and health conditions of the countries of the world in 1956 In the more highly developed countries mortality and the frequency of infectious diseases continue to decrease, but in other countries the increasingly complete statistical information now available reveals serious health problems

In the first part of the report statistics of causes of death have been expanded In the tables on causes of death figures have been given for deaths among young children by sex and by each year of age up to four years A new table on the cause of infant mortality by age has been included Other subjects which have been either expanded or newly introduced are cardiovascular diseases, malignant neoplasms, maternal mortality, and accidents according to the nature of injury In the second part of the volume seasonal statistics of notifiable communicable diseases are given, with the distribution by sex and by age for certain of these diseases

The third part relates to statistics of health personnel, hospital establishments, and vaccinations, and has also been rearranged and extended The number of inhabitants of each country or territory per physician is also given, and the figures show vividly the still urgent need for medical personnel in certain areas of the world

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[1] Third Progress Report of the Standing Technical Committee on Synthetic Detergents H M Stationery Office 1*s* 6*d*

[2] *Annual Epidemiological and Vital Statistics*, 1956 Geneva 1959 Pp 705 £3 Bilingual edition (French and English) Obtainable from H M Stationery Office, P O Box 569, London, S E 1

In England Now

A Running Commentary by Peripatetic Correspondents

LIKE juke-box music, or the melo released at our local this week, or the latest poster for Muck (the anti-cancer cigarette), the annual panorama which the Royal Academy unfolds this week at Burlington House may not be Great Art, but, judging by past experience, it's what we, the public, want And we want these various things for the same excellent reasons The sickly intimacies of the echo-chamber, and the tough mixed-up guy at the cinema, and the cigarette-smoking off-duty Guards major are our beautifying mirrors they reflect, just that bit more poignantly than we could, our numb tastes and aspirations, and they egg us on to put just that bit of extra effort into attaining their unattainable perfection Even those rare birds who pride themselves on being different cannot ignore the common world around them nor—unless they also happen to be provincial parvenus like Horace—would they wish to do so But sadly I must report that that world at present is staunchly unheroic and aclinical (The two always seem to go together perhaps suffering engenders heroism, and heroism causes a great deal of suffering) We, the art-loving public, in 1960 are prosperous, self-satisfied, physically fit, mentally vigorous, and spiritually dull The reclining figures of Henry Moore have no belly and hardly a head But Moore is an artist who is at least both frank and revealing The lesser breed who clutter up the beautifully spacious galleries in Piccadilly paint a face in front of emptiness and wrap a waistcoat with a gold chain or an academic gown around nothing

No crucifixion, no tortured saint, no battles, no road accidents even the modern horrors of the rush-hour underworld look cosy in Jean Clark's "London Travellers" Only Royalty continue to suffer perhaps the public, immune as it sees itself from all infirmities of the flesh, expects them to embody our common ailments as well as our moments of triumph Over the years we have seen them chlorotic, hectically flushed, mildly myxœdematous, dyspeptic, anxiety-ridden, and endogenously depressed But I would not venture to diagnose Epstein's last and rather disturbing offering

To keep clinical interest alive, the less skilful painting creates its own weird and bloodless pathology My own pet anomaly—happily prevalent among debs, duchesses, deans and bishops, headmasters, and chairmen of companies—is carunculosis It consists in a hypnotic prominence of the caruncula of the eyes, and its ætiology is satisfying in its simplicity Or rather lack of simplicity The real artist always simplifies—even at his most representational he has learnt the simple truth that to render a three-dimensional world into two dimensions, and create movement from a piece of stone, he must simplify The dabbler in portrait-painting is far too intent on copying what he thinks he knows must be there to leave anatomy well alone

A single piece of sculpture redeems the display Roy Noakes' "A Woman Reclining"—a wasted, contractured, helpless, hopeless, creature—is a geriatric problem all too familiar It is also a wonderfully moving work of art, made with insight, passion, and compassion

* * *

Now it can be told, says the *D——y M—l*, that during the televised mayhem which causes popeyed viewers to lace their nourishing bedtime cocoa heavily with barbiturates the sounds of fists and blunt instruments colliding with soft tissues is produced by men hitting grapefruits with wooden mallets

It is high time that all TV afficionados said a big "Thank You!" to these dedicated craftsmen as, cramped in some obscure corner of the studio, they keep one eye on the fracas, one on the director, and one on the grapefruit in case someone tries to pinch it (I know, I know, but unless you've got three eyes the job's impossible)

These maestros of the mallet face unflinchingly risks and occupational hazards unique in industrial medicine Apart from doing themselves harm by slipping about on the fruit-skins, they are prone to such traumatic conditions as malletwielder's thumb, an acutely painful syndrome accompanied necessarily by acute retention of expletives.

Also grapefruit often explode on impact, with considerable fall-out; last year the contortions of a TV star who got some juice in his eye earned him an Oscar. Grapefruit percussor's psychosis is believed to be caused by the stemming of aggressive components of the Id during plays with excessive dialogue, and is liable, particularly after political telecasts, to abreact in frenzied episodes in which the patient propels grapefruit in all directions, so that the studio resembles the quarter-deck of Admiral Hornblower's flagship during a close action.

Yet today the grapefruit malleters' morale is high, for these men know they are no longer forgotten. Encouraged by Equity, the British Council has granted £5 million to help produce a semi-documentary feature, "The Ziz Zimmskliski Story", about the most-est grapefruit malleter of them all, whose career ended so tragically when he broke both wrists and his mallet on a grapefruit which had been kept overnight in the deep-freeze.

Production of this epic will start just as soon as somebody discovers how to make a noise like a mallet hitting a grapefruit.

* * *

"Boils" said the patient's mother. "Nothing but boils for months past, that's what we've had. First me mother-in-law, she lives with us, you know, she works at the hospital, she had a boil in her nose. Then Kim and me. Fifteen I've had, one after the other. And poor Kim—pulling her down, it is goodness knows how many she's had. I went to the doctor and he said it was because I was run down. He gave me a tonic. Kim too. But the boils kept coming and he sent me to a skin specialist. He said we were getting them from the cats. He wanted us to get rid of the cats, but we couldn't do that, we couldn't really. Kim's so fond of them. But it's not that, is it, Doctor? It's a germ, surely it must be. It's one of these hospital germs, that's what I said to my mother-in-law. I've done some cleaning myself at the hospital only the doctor said I couldn't continue. I was so run down. It's one of these germs that they get in hospital, that's what I say it is."

Social pathology might be a promising new specialty.

Path. reports

10215	Pus from one of Kim's boils	*Staph. aureus* type 80 resistant to penicillin and to the tetracycline drugs, sensitive to erythromycin and streptomycin
10256	" " another of Kim's boils	
10612	" " yet " " "	
10665	Swab from Kim's nose	
10769	" " " mother's nose	

* * *

A generous donor presented our children's ward with a fine chocolate Easter egg about the size of Humpty Dumpty. So on Sunday at the party, instead of the consultant beaming as Father Christmas, the houseman was given the destructive task of knocking the beautiful creation off the table on to the sheet-covered floor. Like the King's Horses, we failed to put it together again, but we had more excuse, for most of the pieces had disappeared.

* * *

The incidence of medical hagiography
Has a good deal to do with geography.
There are not many Eskimos in Guthrie's *History*,
But what Scotsmen are up to is less of a mystery.

* * *

In the book on child psychology it said that we should avoid making a child afraid of insects, and that a good way of doing this was to say "Hi, Mr. Bug!" in a friendly tone whenever one appeared. We tried this out, and it was very effective—so much so that at the height of summer we found our little girl holding the screen-door wide open and calling to the flies and mosquitoes, "Come in, Mr. Bug!" Which brings me to the point that

Medical psychology
Is different from medical entomology.
Psychology is about projection and cathexis,
But entomology is about infection and anaphylaxis.

Letters to the Editor

LEGAL ASPECTS OF HOMOGRAFTING

SIR,—Professor Woodruff (April 16) has done well to draw attention to the legal aspects of homografting. May I add some observations on bone-grafting in reparative surgery?

Homogenous bone has been used in this way for about half a century, but its widespread application came shortly after the late war when various methods of banking bone were introduced. The Royal National Orthopædic Hospital, for example, has had a bone-bank for ten years.

It has been shown repeatedly that homogenous bone is less suitable as grafting material then autogenous; however, it is not rejected by the body and provides a useful scaffold for the growth of bone from the host. There are circumstances in which bone homografts are indispensable, and for this reason efforts have been made to find the best method for preparing and storing this material. Recently some valuable work has been done at the Institute of Orthopædics by Dr. H. A. Sissons and his colleagues,[1] [2] supported by a grant from the Medical Research Council. They made an experimental comparison of various types of stored homograft and found that freeze-dried bone sterilised by irradiation is a biologically acceptable material. The practical advantage of this method of preservation is, of course, that it permits the use of cadaveric bone, and places storage on a much less precarious footing. Hitherto, unreliable non-cadaveric sources have been almost obligatory—e.g., bone from suitable amputated limbs.

They then proceeded to prepare cadaveric bone for clinical trial, and similar work is already in progress in a number of other countries. Here, in Great Britain, surgeons from a number of other interested centres are anxious to meet to discuss standardisation of methods. It seemed to me that such a meeting should be held under the ægis of the Medical Research Council. But, for the present, it appears that this is not possible because the legality of removal of cadaveric tissues for clinical purposes has come into question. Like Professor Woodruff we are compelled to mark time, though we hope to arrange an informal conference so that when the way is clear it will be possible to go ahead without too much waste of time.

The Ministry of Health and the Medical Research Council are aware of the legal difficulties and no doubt some positive action will be taken before long. It is regrettable that apart from corneal grafting we are six years behind New Zealand, and it is in the interest of many patients that legislation to permit the removal of various tissues from the cadaver for surgical use should be promoted without delay.

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H. J. SEDDON

SIR,—In his letter, Professor Woodruff gives an admirably balanced survey of the present place of homografting in surgery. My own interest is the management of terminal renal failure. I am sure that the renal homograft has a place in treating such cases. It offers a hope of relieving distressing symptoms and extending life, whilst involving no burden upon the patient by way of rigorous medical regime or abnormal mode of bodily function. The main theoretical problem is that of the homograft reaction, and the findings of my registrar, Mr. R. Y. Calne (Feb. 20) studying the effect of 6-mercaptopurine on renal homografts in the experimental animal, have led us to believe that in cytotoxic drugs we have a means of controlling it, possibly more effective and infinitely more acceptable than by irradiation Even so, I would not at this moment hold the homograft reaction as first among the practical problems involved, which are still considerable Since Professor Woodruff has raised the legal aspects, I should like to support his plea for provisions to facilitate this work

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[1] Chalmers, J., Sissons, H. A. *J. Bone Jt Surg.* 1959, 41B, 209.

[2] Chalmers, J., Lea, L., Stewart L., Sissons, H. A. *in* Recent Research in Freezing and Drying (edited by A. S. Parkes and A. V. Smith). Oxford, 1960.

He also mentions appreciation of the situation by members of the public. Whilst still doubtful of the role of public education in medical matters that cannot readily be held to be other than of interest, I believe it to be of value in presenting a new concept in treatment, so that no distorted image should be formed in the public eye This reminds us at once of the need for a most careful and sober presentation, especially of a subject that can easily be dramatised, and I warmly support Professor Woodruff's suggestion of a working party to consider appropriate recommendations

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JOHN HOPEWELL

HUMAN RELATIONS IN OBSTETRIC PRACTICE

SIR,—I am writing to express my delight at reading Prof Norman Morris' views on this subject (April 23, p 913) His article comes at long last to fill a gap which has existed for years As one who has worked as a midwife before working as a doctor, I have had many opportunities of seeing the " sausage machine " at work The surprised and delighted look from a patient addressed by doctor or nursing staff by her name instead of " Mum " or " Mother " was enough to convince one of the need for a change of outlook

The blame for what Professor Morris describes cannot simply be laid at the young doctor's and midwife's door I have witnessed occasions where pupil midwives were severely scolded for " wasting time chattering with patients " when trying to reassure a crying young woman in labour This point of view is still prevalent and changing far too slowly

The interrelationships within the unit are another important point made by Professor Morris I have seen many patients too frightened of sisters or nurses to address a doctor, let alone a consultant. I have also seen " uncooperative " patients being victimised—for instance, by giving them unnecessarily large amounts of aperients, causing sleepless nights, because the sister had them to give at her discretion I remember an occasion when a patient had had so much that she needed a bedpan twelve times during a night, and yet receiving another dose in spite of her complaints

With all due respect for Professor Morris' suggestions for reviewing procedure in clinics and wards, which will certainly do much to improve matters, something more fundamental is needed As long as young doctors, midwives, and nurses are taught almost exclusively about the body, they cannot be expected to understand their patient's minds, with the rare exception of those saying and doing what is right through intuitive insight

What is needed is extensive teaching of dynamic psychology as well as constant discussion of patients and their problems as practical examples to illustrate theoretical teaching Meetings of medical and nursing staff as well as social workers would go far towards teaching all aspects of a case and its problems Such teaching would have to start from the top When I have had to refer neurotic or mentally disturbed patients for an examination, I have encountered more understanding and sympathy in young registrars than in consultants, who often cannot be bothered with frightened patients who hold up a busy clinic

I should like to give an illustrative example from my own psychiatric practice

Some years ago I saw a patient in an acute and severe anxiety state She had not been well since the birth of her child five years previously Her pregnancy had been planned and perfectly normal, and she had been delivered in a private ward of a London women's hospital In spite of being a private patient she had had no attention beyond the most casual care During her puerperium she was very severely depressed and slept little The night nurse did not bother to report this, nor were her depression and general anxiety observed by anyone although she neither ate nor slept well When she came home she had to fight infanticidal impulses for many months, and she never regained her mental health or ability to go back to a normal married life, until she had had a good deal of psychiatric treatment

This woman would have been saved untold suffering if the staff had been trained to observe their patient's behaviour and if the woman consultant had not been completely preoccupied with the patient's tail-end Whilst many doctors and nurses admit that there are emotional ups and down in the puerperium, they are often perfectly satisfied with making such a statement They rarely go on to investigate individual cases, and give that assistance of which these patients are in dire need, even if their disturbance is not as severe as in the above example

London, N W 1
HILDA C ABRAHAM

RED-CELL REGULATORS

SIR,—The volume of publications on this topic in recent years is imposing and makes the reviewer's task a difficult one, but I feel there are several points in your leader of April 9 which should not be allowed to pass without comment

The work of Reissman [1] and Erslev,[2] which gave the first clear demonstration of such humoral regulation, established that the response in the " recipient " animal was an increased production of normal red cells It is clear, also, from the data of Borsook et al [3] that their plasma extracts also evoked " normal " proliferation Since that time intensive studies of the chemical properties of plasma and urine fractions capable of producing this response have shown that a non-dialysable mucoprotein may be derived from either source which fulfils the requirements of these earlier experiments [4–7]

In the very interesting series of experiments by Linman et al which you quote, evidence is forthcoming of a second factor influencing bone-marrow activity, which is thought to be non-protein, and ether-soluble [8] Its effect on recipient rats is characterised by the production of *abnormal* red cells, microcytes with an apparently shortened survival, accompanied by reticulocytosis but no increase in hæmoglobin [9] From their data it is apparent that this factor is demonstrable in conditions where there is hyperplasia of the marrow, including both primary and secondary polycythæmia, and also where there has been suppression of mitosis by X-irradiation [10] or by ^{32}P therapy in polycythæmia vera [11] They conclude, perhaps somewhat hastily, that this factor is " not a by-product of hyperactive myeloid elements ",[11] and that it is of ætiological importance in polycythæmia vera However, an alternative hypothesis suggests itself—that it may be a factor formed in the normoblast in the premitotic phase stimulating D N A synthesis, acting on other normoblasts if it should pass out of the cell, and that it might continue to be liberated by cells in which radiation

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1 Reissman, K R *Blood*, 1950, 5, 372
2 Erslev, A J *ibid* 1953, 8, 349
3 Borsook, H , Graybiel, A , Keighley, G , Windsor, E *ibid* 1954, 9, 734
4 Rambach W A Alt, H L , Cooper, J A D *ibid* 1957, 12, 1101
5 Gordon, A S , Winkert, J W , Dornfest, B S , LoBue, J , Crusco, A *in* The Kinetics of Cellular Proliferation, p 332 London, 1959
6 Jacobson, L O , Goldwasser, E , Gurney, C W *ibid* p 344
7 Borsook H *ibid* p 357
8 Linman, J W , Bethell, F H , Long, M J *J Lab clin Med* 1958,
9 Linman, J W , Long, M J *Blood*, 1958, 13 226
10 Linman, J W , Bethell F H *ibid* 1957 12, 123
11 Linman, J W , Bethell, F H , Long, M J *Ann intern* 51, 1003

damage prevents the orderly synthesis of D N A There is some evidence that humoral factors may be found in urine of patients with lymphatic reticuloses and chronic lymphatic and myeloid leukæmias which stimulate increased production of lymphocytes and polymorphs respectively [12] and these factors may be biologically analogous Such a view of the origin of these factors is consistent with a neoplastic concept of these diseases

There is an increasing body of evidence to suggest that the mucoprotein factor is the basic regulator of erythropoiesis Erslev [13] has put forward evidence that the physiological regulator operates as a stimulus to differentiation in the "stem cell" rather than influencing rate of mitosis in later normoblasts and Alpen and Cranmore [14] have shown that the intermitotic interval of nucleated red cells in normal and anæmic dogs is the same Alpen and Lajtha [15] have failed to show any acceleration of maturation or hæm synthesis in vitro in marrows incubated with a potent mucoprotein preparation of Van Dyke, whilst Gordon has shown a similar preparation to increase red-cell production in the isolated hind limb of the rat [5] It seems likely, therefore, that this factor influences hæm synthesis only by the production of an increased number of early normoblasts, a view which Linman now accepts [16] It is then to the mucoprotein factor that attention should be turned in polycythæmia vera, if the condition is believed to be caused by a disorder of physiological control, and here you misquote Linman et al [11] After 14 days injection of extracts, increased red-cell and reticulocyte counts were observed, but *no evidence is offered of increased hæmoglobin values in the* recipient animals In discussion they comment that "augmented amounts of the humoral agent which enhances hæmoglobin synthesis are also detectable" and the crux of the argument is the method used for assay of this agent Their data are summarised below

Korst et al [17] described an assay method using rats in which mitosis had been partially suppressed by nitrogen mustard In clinical assays they showed stimulation of iron utilisation by plasma from two cases of primary polycythæmia, but no stimulation by plasma from three cases of secondary polycythæmia More recently [18], they reported *a series of assays measuring iron* utilisation in starved rats, and find that the *mean* iron uptake in rats treated with plasma from patients with both primary and secondary polycythæmia is greater than the mean of the control values, but do not state whether the *difference was significant The stimulation produced by these plasmas* was considerably less than that produced by plasma from anæmic animals

The former assay might be expected to respond to general stimulants of mitosis and possibly to certain nutrients for D N A synthesis The metabolic complexity of the fasted animal makes it difficult to evaluate minimal changes

In our laboratory, we have used rats for assay which have been rendered polycythæmic by injected red cells—chosen because they might be expected to lack specifically the physiological stimulus to erythropoiesis This preparation is responsive to whole plasma, and to mucoprotein concentrates from plasma and urine of anæmic subjects with both hyperplastic and hypoplastic marrow [19] Stimulation of iron utilisation may be readily demonstrated following injection of plasma samples from patients with secondary polycythæmia but not with whole or greatly concentrated fractions of plasma from patients with polycythæmia rubra vera, thus casting grave doubt on the significance of findings mentioned above Rimington and Nizet [20] have demonstrated yet another humoral agent in "anæmic" plasma which is ultrafilterable and active in vitro in stimulating hæmoglobin synthesis Nakao et al [21] present data which further delineate this from the mucoprotein factor, and this may also prove to be an intracellular normoblast metabolite or enzyme liberated into plasma, further findings in this field are awaited with interest This factor may influence certain of the reported assays based on iron utilisation, but, as ultrafiltrates from highly "potent" plasmas are totally inactive in the polycythæmic animal, it seems unlikely that we are being *misled by it*

We have confirmed the presence of the ether-soluble "erythrocytosis" factor in polycythæmia vera [19] and it seems reasonable to suppose that it plays some part with the other "lipid" factors [11] in producing the peripheral blood changes in polycythæmia (the microcytosis and possibly the mild white-cell and platelet elevations which often occur) However, caution should be exercised in accepting the view that changes in these factors are the primary cause of the polycythæmia.

Finally, since on present data both the mucoprotein factor [4] and the ether-soluble factor [8] may produce reticulocytosis in the normal animal, it seems unwise to grace with the term "erythropoietin assay" procedures based on this parameter alone Osnes [22] demonstrated raised hæmoglobin values in his mice, but uses reticulocytosis alone in his routine experimental and clinical studies The fact that Jones et al [23] find lower values in renal venous than mixed venous blood in their cases of renal polycythæmia is in keeping with the view that they are predominantly demonstrating the lipid factor—the result rather than the cause of the polycythæmia The slow return to normal values on assay after nephrectomy is again consistent *with this interpretation*

Many American workers have applied the term "erythropoietin" to the mucoprotein factor,[6] the production of which appears to be intimately related to the kidney and it seems to be confusing to apply it now in a different context

That reticulocytosis may be governed by other factors than those influencing erythropoiesis has been pointed out by Gordon [24] who showed that bicarbonate alone produced a reticulocytosis when injected into a hypophysectomised animal One would like to see more than a 3% reticulocytosis produced by a plasma ultrafiltrate in an acidotic animal as clear evidence of a further independent renal erythropoietic factor [22]

The London Hospital, E 1 D G PENINGTON

PALLIATION IN MALIGNANT STRICTURE OF THE ŒSOPHAGUS

SIR,—The letter of Mr Jamieson and others (April 23) seems to confirm our experience of the Mousseau-Barbin tube We have met the following difficulties and complications in the use of that 'Neoplex' tube

(1) The catheter portion is too soft for easy introduction, on the other hand, the use of a metal introducer makes the procedure rather dangerous The only safe method seems to be a railroad one not unlike Mr Moghissi's manœuvres

(2) The lumen is too small and tends to block easily We had a *patient who drowned himself after drinking a cup of milk* at the end *of a meal consisting of semi-solid food*

(3) The tube rides up during the act of vomiting

(4) The V-shaped funnel gives rise to an annular ulcer and to submucosal œdema above it—sometimes gross enough to cause complete dysphagia

(5) *Many patients were acutely aware of the presence of* a foreign body in their œsophagus In some the distress was worse than the preoperative symptoms The lack of resilience of the tube and the shape of its funnel are the probable cause of this

These points prompted us to devise a tube [25] that is more resilient, has a large lumen, carries a tulip-shaped funnel, can be stitched in position, and is in two parts *that* facilitate introduction under direct vision

This tube has now been in use for over eighteen months No ulceration or erosion has yet been met Some senile patients tend to indulge in foods that may lead to temporary blockage of the tube—this is the exception rather than the rule. The œsophagus was transgressed in one of the intubations as a right pleural effusion followed the operation. No patient has as yet been troubled by retrosternal pain after intubation. Two patients with a broncho-œsophageal fistula have benefited from the operation. The tube has not been used in the treatment of benign strictures, but was used to relieve dysphagia in two patients with extraluminal tumours (bronchial and mammary mediastinal secondaries). The survival time ranged from two weeks to ten months. In all, 17 patients have been intubated. Biopsy confirmation was obtained in every case.

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L. R. CELESTIN

THROMBOPHLEBITIS FOLLOWING INTRAVENOUS INFUSION

SIR,—In your leader of April 23 you list as causes of thrombophlebitis following intravenous infusion (1) venous endothelium torn by needle point, (2) low pH of infusion fluid (doubtful), (3) duration of infusion (very important), (4) nature of tubing used. A possible addition is local sepsis or a coagulase-positive staphylococcus, or its exotoxin, in the infusion fluid.

You mention the work of Cruickshank et al.[1] who estimated the power of the unknown toxic substance released from tubing, by its effect on tissue cultures. You agree that the toxicity revealed by these tissue-culture tests is of clinical importance, but add that something equally effective but much simpler in technique is required for routine use.

I would like to suggest that the free-living forms in ordinary pond water could be used as test animals. Suitable short lengths of different varieties of rubber tubing could be firmly clipped, filled with suitable water, clipped again at the top, suspended overnight, and then the water from the interior of the clipped length of tubing allowed to flow into a watch-glass containing a selection of the active pond denizens. Their reactions can then be watched under the low power of the microscope.

This idea is not entirely original as will appear from a paper[2] on the mortality of aquatic insects and fishes caused by the use of latex tubing in experimental apparatus by J. W. DeWitt.

Pathology Department,
St. Margaret's Hospital,
Epping.

FRANK MARSH

MONDAY-TO-FRIDAY WARDS

SIR,—The hospital scene is constantly changing as new treatments and new drugs alter clinical needs. Over the past thirty years the fever hospitals have almost emptied, now the sanatoriums are gradually emptying; tomorrow, if present trends continue, it may even be the turn of the mental hospitals. But besides these medical changes the hospital must also face social changes.

Mr. Stallworthy (Jan. 9) has pointed out the fantastic costs of the hotel services which the hospitals are providing. At the start of the century people accepted the idea that hospitals were mainly for the homeless, friendless, or very poor. Those who were not in such need nursed their sick at home. Surgeons performed tonsillectomies on kitchen tables, mothers hung sheets soaked in carbolic lotion in front of the bedroom door of the child with measles. Yet this was before electricity, and often before w.c.s, came into the home. Modern conveniences, light, and space in council houses would make treatment at home a reasonable proposition for many patients, if it were supported by flying squads of doctors and nurses with adequate mobile equipment. What a saving of bills for food, service, heating, wear and tear of bedding, cleaning materials.

Another insidious change has been observed by those of us who have spent a working life-time in hospitals—the growing dearth of spinster nurses due to a high marriage-rate and the early age at which girls now marry. This will be felt even more acutely in a few years, as the old spinster sisters and matrons die or retire. If, as happened in Victorian times, it becomes the fashion for girls to marry at 17 or 18, there will soon not even be spinster student nurses.

Will the hospital of the future solve its problems by having some Monday-to-Friday wards? Obviously some patients will need inpatient care at the weekend, but would it be beyond the powers of clever organisers to arrange for the others—I would suggest as many as two-thirds—to spend the weekend at home? Will the day come when private cars and ambulances arrive at the hospital to take patients home at 5 P.M. on Fridays and return them at 9 A.M. on Mondays?

Ranworth, Notts.

MARIE A. SIMPSON

KEROSENE (PARAFFIN) POISONING

SIR,—The recent correspondence on poisoning by the ingestion or inhalation of domestic paraffin is of particular interest to those who practise in rural areas, since such poisoning constitutes a real, albeit diminishing, danger to small children. The higher standard of living of farm-workers and the increasing use of electricity in the country mean that less paraffin is used in the house, but it is used for various purposes on the farm, and some households still prefer it for its cheapness and are loth to part with their paraffin stoves. Unfortunately the oil companies have made it much more attractive of recent years by colouring it pink, blue, &c.

As one hazard shows signs of diminishing another appears to take its place and more recently the ingestion of furniture and floor polishes of various types has taken the place of paraffin poisoning as a cause of admission to the pædiatric wards in Lincolnshire. These substances are not thought of as dangerous in the average household and hence are not kept out of the way of young children.

It is surprising how often paraffin, and even petrol, are kept in bottles which have contained milk or soft drinks, or else in jam jars, and I now always inquire what kind of receptacle the paraffin was in. In one case a blue teapot containing paraffin was kept permanently on the hearth to revive the fire whenever necessary, and a child of 1 year 11 months who put her lips to the spout and drank an unknown quantity became so seriously ill that she was in a coma for five days. In a rapidly fatal case of petrol poisoning a child drank petrol from a jam jar on the floor of a garage while his father was carrying out repairs to the engine of his car within a few feet of the child.

I agree that the margin between the amount needed to produce unconsciousness and the amount required to kill is small, particularly as the victim is usually a child of less than 2 years. In a series of cases treated at Boston General Hospital between 1950 and 1955 the youngest was 1 year 2 months and the oldest 1 year 11 months.

On balance I think it is probably safer to wash out the stomach and risk a chemical pneumonia from inhalation. The alternative is coma, not unlike that of acute alcoholism, and gastrointestinal irritation. Nevertheless the chemical pneumonia produced by inhalation of paraffin or similar substances may take a very long time to resolve and does not always respond to antibiotics. Two of our cases still had demonstrable shadowing in the X-ray film of the chest after a month and another had a relapse of pneumonia 3 months from the date of poisoning. We have sometimes been surprised at the extent of the shadowing seen in the X-ray film compared with the paucity of physical signs on auscultation of the chest.

In the pædiatric service of South Lincolnshire Dr. Trevor Wright and I now regard the ingestion of paraffin or allied substances as a medical emergency requiring admission and energetic treatment. Experience shows that these chemicals are much more toxic than might be anticipated.

Boston General Hospital,
Boston, Lincs.

I. M. CULLUM

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[1] *J. clin. Path.* 1960, 13, 42.
[2] *Science*, 1957, 126, 840.

EARLY TREATMENT OF STOVE-IN CHEST

SIR,—The wisdom of Mr Barrett's advice (Feb 6) on the management of severe chest injuries is the more pertinent because it underlines once again the vital need for surgeons of the widest experience if we are to do justice to the management of multiple injuries Patients given adequate blood-transfusions seldom die from limb injuries, but they are often lost from respiratory embarrassment or damage to other vital organs, such as the brain and liver It is surprising therefore that a general anæsthetic in the casualty department should be seriously advocated for the immediate treatment of a patient who amongst other injuries may have a flail chest

It is a fundamental principle in the management of the critically injured that after a free airway and transfusion are established, repeated examination is the next priority, particularly in the assessment of brain and abdominal injuries The administration of a general anæsthetic in a changing situation, frequently associated with injuries to the face, will daunt any but the most intrepid and carefree anæsthetist The surgeon will be no less worried because of the possibility of other injuries

That a tracheostomy and controlled respiration are lifesaving on these occasions is plain for all to see, but why not use local anæsthesia with the head and shoulders raised to relieve venous congestion? The patient will thus remain conscious and allow more mature assessment after control of his respiration

Department of Surgery,
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EDWARD ALLCOCK

PIPERAZINE ADIPATE IN HETEROPHYES HETEROPHYES AND OTHER HELMINTH INFECTIONS

SIR,—We found[1] that piperazine adipate and citrate were effective in *Heterophyes heterophyes* infections in divided doses of 12 6 g and 14 g respectively over 7 days Larger trials were undertaken to confirm these findings We studied the effect of piperazine adipate ('Nometan') in *Heterophyes heterophyes* infections in patients from the outpatient clinic of the rural health unit at Ezbet-El-Burg, near Damietta, an endemic focus of this infection

Twenty patients were treated with piperazine adipate (0 3 g tablets) Their ages ranged from 6 to 50 years and they were between 20 and 80 kg in weight The dose varied between 0 9 and 4 5 g daily over a period of 2–10 days The total dose ranged from 6 3 to 22 5 g

EFFECT OF PIPERAZINE ON VARIOUS HELMINTH INFECTIONS

Infestation	No of cases treated	Total dose of piperazine (g)	Duration of treatment (days)	Cured cases
Heterophyes	20	6 3–22 5	2–10	11 (*55%*)
Ascaris	3	6 3–18	4–7	3 (*100%*)
Trichocephalus	2	6 3 & 12·6	7	2 (*100%*)
Trichostrongylus	1	21 3	6	1 (*100%*)
H nana	1	18 9	7	0
Enterobius	1	18 9	7	1 (*100%*)
Ancylostoma	1	6 3	7	0

Eight of the twenty cases stopped passing ova after 4–5 days' treatment, and another three patients stopped passing ova after 6-7 days' treatment. The other nine patients continued to pass ova despite treatment.

Two patients infected with trichocephalus (one concurrently with heterophyes and the other with ancylostoma and ascaris) were treated with 12 6 g and 6 3 g respectively In both cases stools were negative for trichocephalus, heterophyes, and ascaris but ancylostoma ova continued to be passed

One patient who was infected with heterophyes and trichostrongylus took 21 3 g of the drug over 6 days After 3 days trichostrongylus eggs were no longer passed, but those of heterophyes were still passed in spite of the large dose given

One patient infected with enterobius and *H nana* concurrently with heterophyes received 18 9 g over 7 days Tests were negative for enterobius after 7 days, but the other eggs continued to be passed

Side-effects of the drug were slight except in those taking more than 3 6 g daily, in whom there was slight dizziness The general condition of all patients improved colicky pains subsided and appetite increased

Follow-up stool examinations were done every other day for one month

Department of Parasitology,
Faculty of Medicine, Ein-Shams University,
Cairo

H F NAGATY
H. M. KHALIL

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[1] Nagaty, H F, Rifaat, M A, Salem, S *Lancet*, 1955, ii, 827

GENETIC TERMINOLOGY

SIR,—Professor Penrose (April 9) is perhaps unduly harsh in calling your terminology inaccurate As regards "sib" or "sibling", it is the form you used, "sibling", which had the more precise and restricted meaning of "a relative" in Old English, and which is given in its scientific sense in the 1933 supplement of the Oxford English Dictionary However, "sib" is shorter and gaining ground with geneticists

As regards "monozygous" or "monozygotic", the difference appears to be between the present participle and the verbal adjective, which here has the meaning of the perfect passive participle Since the fusion of germ cells precedes the twinning, "monozygotic" is more correct, and is given in the 1933 supplement But it is an ill-sounding word, and "monozygous" is used in at least two recent textbooks It would be nice to hear from a Greek scholar whether the frequent, but exact, use the Greeks made of the present participle could justify "monozygous"

Orpington

C O CARTER

LUNG CANCER AND TOBACCO MOSAIC VIRUS

SIR,—I do not seem to have explained (March 26) clearly enough the assumptions that have to be made before the idea that tobacco mosaic virus (T M V) is a cause of lung cancer (as proposed by Dr Bothwell in his letters of March 19 and April 23) can be accepted Lest silence should be interpreted as agreement with the new statement of the idea, I will try to be both brief and more explicit

We may accept, for the sake of argument, the idea that specificity resides in nucleic acids, it has to reside in something and they are no less probable than any other type of molecule. In theory they offer superabundant possibilities for specificity, no two particles of nucleic acid that have so far appeared on Earth, if they have the complexity generally accepted, need have been identical The idea that nucleic acids carry specificity, or in modern jargon "information", in the cell, pre-supposes that there is an immense number of different nucleic-acid structures or configurations in each cell The observation that viruses maintain some continuity in their properties suggests that, if nucleic acid is the material controlling these properties, its constitution remains fairly constant From these two propositions it follows that infection with T M V adds little to the pre-existing complexity of the nucleic-acid pattern of the tobacco plant

Only in exceptional or long-established virus infections—e g, some warts—does the amount of anomalous nucleic acid in the infected cell approach the amount of normal nucleic acid Most of the nucleic-acid breakdown products absorbed through the smoker's gut or lung will therefore be derived from normal tobacco nucleic acid rather than from T M V Foodstuffs contribute still more "foreign" nucleic acid—often in a pyrolised state

The idea that the breakdown products of virus nucleic acid are in some way special and more likely than those of any other sort of nucleic acid to be carcinogenic is, on present evidence, simply alchemy It depends on the old assumption that there must be chemical similarity between substances having analogous biological effects Obviously the absence of evidence does not demonstrate that T.M.V. has nothing to do with lung cancer My contention is only that the breakdown products of T.M.V. are no more likely to be involved than those of any other component of the tobacco leaf I will go further, and suggest that there is no reason to think that, if people smoked hay, they too would not have an increased lung-cancer rate

Rothamsted Experimental Station, Harpenden N W PIRIE

EFFECT OF BEER ON BLOOD FIBRINOLYTIC ACTIVITY

SIR,—The article of Jan 23 by Dr Fearnley and his colleagues is perhaps bad news, since it suggests we must now deny patients who are poor coronary risks this seemingly innocuous beverage

The authors consider it is not the alcohol, but some substance produced during fermentation which reduces the blood fibrinolytic activity As they used English draught beer, which is unpasteurised and only partially filtered, it is possible that this substance, whatever it is, may not be present in pasteurised and highly filtered bottled beer All bottled beer is, I believe, pasteurised to prolong shelf-life, but it varies in gravity, colour, and lightness in different countries Before concluding that *all* beer is potentially harmful in this regard would it not be interesting to test samples from some of the main beer-drinking countries of the world? I should be very glad, should Dr Fearnley desire, to send him a quantity of pasteurised, double-filtered Canadian-bottled beer—strictly for experimental use, of course!

Mount Royal, Montreal PETER H NASH

THE SHORTAGE OF NURSES

SIR,—There is a serious shortage of nurses in our hospitals For this reason wards are closed Some nurses are overstrained by their work and some have to take responsibility which ought to be carried by their seniors In such a situation efficiency must suffer and an unregulated service develop Not only is efficiency reduced but anomalies arise. Thus in some hospitals ward orderlies may receive, with overtime, a larger weekly salary (excluding superannuation) than the ward Sister herself

But the nursing problem is not really a problem of money, though money can aggravate it and create a sense of injustice.

Many trained nurses are lost to the profession in Great Britain because they emigrate. More than 2500 nurses emigrated in 1958 If this is prompted by the adventurous spirit it should not be discouraged, but if it is the result of unsatisfactory conditions in this country a remedy should be sought without delay In addition, many nurses are required for industrial undertakings, so that, although the total number of nurses has increased, the demands have increased also

How can this state of affairs be remedied? Everybody must recognise that the care of the sick cannot take a second place. The first step should be a getting together of the various bodies concerned to consider what shortages actually exist and the possible ways of meeting them It may be said that this is a task for the Ministry of Health alone, but this Ministry, although it may have the power, has, where possible, probably wisely preferred to rely on giving advice rather than on issuing orders

In these circumstances a central body consisting of representatives of the Ministry of Health, the hospitals themselves, the British Medical Association, and the Royal College of Nursing seems to be the obvious means of attacking this national problem If a new approach were made, pointing out the tremendous claim the sick have on our good will and the duty of the community to provide care and attention for them, the appeal should not be in vain The time is specially advantageous for it because an increasing number of girls are and will be reaching school-leaving age and looking for worth-while careers

This central body should be concerned not only with recruitment but also with amenities and accommodation for nurses and with incentives to take the less attractive posts I should like to see a proportion of the annual budget for hospitals reserved for replacement or improvement of any nurses' accommodation which is substandard and needs upgrading At present, such accommodation has to take its place in the queue, and its claim may have to give way to those of buildings obviously needed for the direct use of patients Yet on the welfare of the nurses everything else in a hospital ultimately depends

The present situation has continued far too long If patients are to be properly cared for, it must be dealt with as an urgent matter

Nottingham S ALAN S MALKIN

MOUNTAINEERS AND MEDICINE

SIR,—I shall certainly refer to Dr Horniblow's interesting article of April 9 when next asked to advise a mountaineering or jungle expedition Some things occur to me as worth adding

There may be something to be said for two medical examinations the first, of all potential members of an expedition far in advance of the departure date to look for conditions which would absolutely bar a man from going, and the second, of the final team (and any first " reserves ") much nearer the departure date to look for such things as upper respiratory tract infections and fungal infection of the feet. These may then be dealt with in preparation for the departure and, if need be, treatment continued on the way While a chest radiograph is advisable, it should not be said that it will exclude bronchiectasis Only a good bronchogram would do this, but this procedure need not be advised for all mountaineers! A careful history and clinical examination should suffice.

Dimethylphthalate (D.M.P.) is rarely mentioned in books and articles which call attention, sometimes in dramatic terms, to the discomfort of insect bites It is cheap and easy to carry in the pocket and effectively abates attacks by many insects, thus reducing, at least to tolerable levels, skin irritation and infection A newer and, it is claimed, better substance for this is diethyltoluamide.

Two pairs of properly fitting woollen socks and boots are to be recommended An expedition's medical officer, however well he thinks he knows the expedition members, would be wise to inspect everyone's feet daily There is a great temptation, after a long march, to wash the feet and then expose them and even to walk about barefoot. This should be forbidden Insect bites and stings, thorns and cuts, apparently trivial at the time, are potentially very troublesome Dr Horniblow, having been to the Himalayas, does not mention that fearsome foot pest of Africa and South America, the chigoe flea (*Tunga penetrans*) The gravid female of the species burrows into skin of the feet and there swells with the multiplication of young Early excision is the treatment and there are those who still insist that only the local inhabitants know how to do this properly

The response of infected blisters to vitamin C is of interest On the assumption that all members of an expedition are fit and have a full " reserve " of vitamins before they start, one tends to advise against adding to the luggage by taking vitamins (sometimes to the chagrin of the expedition and its benefactors who tend to regard them as essential or at least as "pep" pills) Perhaps one should make an exception of vitamin C if the expedition is to be away for several weeks

Most sore throats at high altitude are, I agree, probably due in the first place to the physical trauma of panting in cold dry air One wonders whether lozenges, as often recommended, apart from the local anæsthetic action some of them may have, may not work simply by keeping the mouth shut!

Piles, especially painful external ones, can add greatly to the miseries of being at high altitude The affliction is common enough to warrant taking an ointment for their specific treatment—especially one containing a local anæsthetic This can be a great comfort too on raw surfaces from broken blisters

A careful calculation should be made of what analgesics may be required Headache is very common at high altitude and contributes much to the discomfort of fitful sleep The demands for relief may be considerable, and woe betide a medical officer who soon runs out of aspirin!

London, S W 14 HENRY BUNJÉ

ORAL HYPOGLYCÆMIC AGENTS

SIR,—*Your leading article* [1] which compares tolbutamide and chlorpropamide in the oral treatment of diabetes mellitus reveals erroneous statements of fact and consequently arrives at amazingly false conclusions

You state quite correctly that for all new agents "the standard of reference is insulin" Since in your words "the main criterion will be the relative toxicity" you should be aware of the serious toxic effects of chlorpropamide in the American experience

The incidence of jaundice runs about 0 4% with 2 fatalities in 5000 patients according to the manufacturer's admission, others estimate this complication at 1% In my own personal experience with over 3000 patients treated with tolbutamide I have never encountered a single instance of hepatic dysfunction let alone overt jaundice On the other hand, 6 patients out of 400 treated by me with chlorpropamide developed serious disabling jaundice Yet you state that chlorpropamide obstructive jaundice "seems to be less common than with tolbutamide" If the more than 500,000 patients now using tolbutamide in America were to be transferred to chlorpropamide then I would expect as many as 200 deaths in addition to thousands of instances of jaundice In this city 2 patients succumbed recently to jaundice and bloody diarrhœa after three weeks of chlorpropamide (250 mg daily) 1 of these patients died of this syndrome Since the obstructive jaundice characteristic of chlorpropamide is, in the opinion of most liver pathologists, not related to dosage but to drug idiosyncrasy you can appreciate my anxiety about wider public use of this agent The 2 cases I cited above reflect this lack of correlation to dosage

The severity of hepatic toxicity and the appreciable side-effects of severe hypoglycæmia make it impossible for me to see any advantage of chlorpropamide over tolbutamide In fact, since the American experience with tolbutamide is remarkably free from either hazard, in good conscience it should be preferred invariably to chlorpropamide There can be no compromise with safety

Mount Sinai Hospital,
New York HENRY DOLGER

⁂ When we said "these seem to be less common than with tolbutamide," we were referring only to gastrointestinal disturbances, and we apologise for not making our meaning plain Dr Dolger seems to have been unfortunate in meeting 6 instances of serious jaundice among 400 patients treated with chlorpropamide The incidence of jaundice recorded in the symposium published last year in the *Annals of the New York Academy of Science* was only a fraction of this Hamff et al [2] described 3 diabetics who developed jaundice during treatment with chlorpropamide, and after recovery 2 of them were given chlorpropamide again without ill effect, suggesting that the drug may not have been responsible in the first place Others [3,4] have even claimed that chlorpropamide may protect against liver damage in man and rats, and Heinsen [5] noted recovery from severe jaundice when a diabetic was given chlorpropamide instead of insulin.—ED L

BISALBUMINÆMIA

SIR,—We read with interest Professor Wieme's comments (April 9) on our paper on bisalbuminæmia While his suggestion of a sickle-cell-trait analogy is intriguing, we would like to point out that in the sickle-cell trait, the proportion of abnormal hæmoglobin can vary between 22% and 45% of the total hæmoglobin, whereas in bisalbuminæmia the abnormal protein appears to regularly constitute about 50% of the total albumin

Chemical Pathology Department,
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London, S W 1 *GEOFFREY FRANGLEN*

AXILLARY LYMPH-NODES IN PATIENTS WITHOUT BREAST CARCINOMA

SIR,—Mr McNair and Mr Dudley showed, in your issue of April 2 that one-third of normal axillæ have palpable lymph-nodes, and they have thereby placed an item of common clinical experience on a sound statistical basis They rightly deduce from this that the common method of staging breast cancer is inaccurate I can go further and state that 50% of breast cancers are incorrectly staged, pathologically To do so, I will first have to make four premises whose contained facts will not be disputed, though the exact percentages quoted may be open to discussion

(1) In a series of breast cancers, about 40% present as Manchester stage I

(2) As McNair and Dudley have shown, 33% of cases placed in stage II, are in fact stage I (false positive)

(3) Where lymph-nodes are clinically not palpable, they will in fact contain growth microscopically in 40% (false negative)[6]

(4) Wangensteen [7] states that 60% of patients in whom the axillary nodes are definitely involved will have occult or overt metastasis in supraclavicular or anterior mediastinal nodes, or both (thus placing them in Manchester stage IV)

Therefore, of every 100 cases of breast cancer, 40 will not have palpable nodes in the axilla Of these, 16 (40%) will have microscopic metastases Of the remaining 60, 10 will be stage IV, by virtue of distant metastases and cannot enter into the discussion Of the 50 in stages II and III 17 (33%) will be incorrectly staged (false positive) Of the remaining 33, 20 (60%) will be too optimistically graded because they will have supraclavicular or anterior mediastinal metastases To summarise

100 cases	40 stage I	*16* false negative 24 genuine
	50 stages II and III	*17* false positive *20* false negative 13 genuine
	10 stage IV	

Therefore a total of 53 cases have been incorrectly staged This statistical juggling is pleasant mental exercise, but does the conclusion affect our comparisons between different treatment series, or even the prognosis in any given case? The answer is probably *no*, because all series contain the same errors in roughly the same proportions

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[1] *Lancet*, 1959, ii, 1129

[2] Hamff, L H., Ferris, H A , Evans, E C , Whiteman, H W *Ann NY Acad Sci* 1959, 74, 820

[3] Leevy, C M , Tornow, A , Greenberg, P , Zinke, M *ibid* p 725

[4] Knick, B *ibid* p 858

[5] Heinsen, H A *ibid* p 709

[6] McWhirter, R *Brit J Radiol* 1955, 28, 128

[7] Wangensteen, O M *Surg Clin N Amer* 1956, 36, 1051

Leicester General Hospital I G SCHRAIBMAN

BRETYLIUM TOSYLATE IN THE TREATMENT OF HYPERTENSION

SIR,—Recent correspondence in your columns,[1–5] following the report from Hammersmith by Dollery et al,[6] prompts us to comment on our experiences with the treatment of hypertension in an African hospital in East Africa

Although the larger proportion of patients treated at our hypertension clinic present with hypertensive heart-failure, in approximately two-thirds of all patients the hypertension is due to chronic renal disease [7, 8] The mainstay of our treatment is ganglion-blocking therapy in the form of pempidine ('Perolysen') We have also tried adrenergic blockers and so far we have treated 20 patients with bretylium tosylate ('Darenthin') and 25 patients with guanethidine ('Ismelin') for periods of up to four months

Using bretylium, the Hammersmith workers found an unsatisfactory response in malignant hypertensives, in 5 of whom a daily dose of 2400–3600 mg with added chlorothiazide proved ineffective Overall, they obtained satisfactory response in 75% of their patients Our experiences have been less encouraging, and in this respect we share the views expressed by Turner and Lowther [1] Patients transferred from pempidine have felt greatly relieved of side-effects of ganglion-blockade at the expense of inadequate control of their blood-pressure Tolerance has developed rapidly and it has not been unusual, in our patients, to reach a daily dose of 3000 mg with added reserpine within a week of commencement of therapy without achieving adequate control of blood-pressure Thus we have reverted to pempidine in resistant cases

The following case illustrates extreme resistance to bretylium

A 25-year-old Ganda male tradesman was admitted in hypertensive heart-failure of two weeks' duration Blood-pressure was 200/160 mm Hg An additional complaint of painful micturition was found to be due to a chronic urethral stricture

Investigations—Hb 13 6 g per 100 ml Urine moderate proteinuria, many red cells and pus cells in deposit Urine concentration to 1010 Blood-urea 42 mg per 100 ml Intravenous pyelogram, poor excretion, no hydronephrosis E C G and X-ray of chest, compatible with gross left ventricular hypertrophy

Treatment was begun with digoxin and hydroflumethiazide Adequate blood-pressure control was effected with pempidine 10 mg eight-hourly Standing B P readings were 130–140/90–100 Because of persistent abdominal distension and early ileus, he was transferred to bretylium, starting with 200 mg eight-hourly Meanwhile he was also undergoing various stages of operative treatment for his urethral stricture under chemotherapeutic cover

Resistance to bretylium was evident from the outset Despite added reserpine and increases of the dose of bretylium, his blood-pressure remained in the region of 220/130 Four weeks later his daily dose of bretylium had reached 18 4 g He felt profoundly weak Blood-urea was 87 mg per 100 ml The standing B P was 170/150 His suprapubic cystotomy had become infected with *Pseudomonas pyocyanea*, coliforms and proteus He was changed to guanethidine 25 mg eight-hourly but no improvement was noted in his blood-pressure reading for the next three days On the third day he died, presumably of severe urinary sepsis Postmortem examination was refused

Had he survived, it is possible that response to guanethidine would likewise have been unsatisfactory He had not received oral diuretic agents latterly We have now begun attempts with added chlorothiazide in all patients receiving bretylium and it is our preliminary impression that the combined regime is likely to be more satisfactory

So far we have not recorded any major side-effects with bretylium except for postural giddiness in 2 patients In none have we noted exertional hypotension as reported by Lowe and Rosenheim [3]

We wish to endorse the view that greater care is required in the use of adrenergic blockers than with the established ganglion-blocking agents Their action and fate, particularly in hypertension due to chronic renal disease, needs further observation and investigation

Makerere College,
University College of East Africa,
Department of Medicine,
Kampala, Uganda

K SOMERS

MATERNAL INFLUENZA AND CONGENITAL DEFORMITIES

SIR,—Dr Trimble (Jan 9) points out that Dr Coffey and Professor Jessop's findings [1] of an increase in congenital malformations in Dublin infants whose mothers suffered from influenza early in pregnancy is not in accord with the results in similar investigations in Iowa [2] and Los Angeles [3] Although the case and control sampling in the American studies is by no means unassailable, Dr Trimble suggests that the reason for the difference is to be found in the criteria for diagnosis in the Dublin investigation, these criteria were, he believes, inadequate In making this inference he himself is committing an error

If he were setting out to investigate the effects of virus infection during pregnancy on the young of a species of experimental animal, I am certain Dr Trimble would take care to ensure that the genetic strain, the diet, the room temperature, and all the other variables in his controls were as similar as he could reasonably contrive to those in his experimental groups so that the groups would differ in only one respect—infection In human work such control cannot be carried out, but it is part and parcel of modern epidemiological method to try to match control and experimental groups as closely as possible Similarly when comparisons are made between two separate studies, whether experimental- or epidemiological, the significance of any environmental factors should be borne in mind

Setting aside the difference in rainfall, temperature, and hours of sunshine between Dublin on the one hand and Los Angeles [3] or Iowa [2] on the other, the fact that Ireland is a country perplexed by emigration, whereas in the United States—and particularly California—immigration is the chief concern, is germane to the present argument The incidence of congenital abnormalities in Dublin (16 per 1000) is known to be high, and anencephaly in particular is a problem there [4] Coffey and Jessop in their earlier investigations [4–6], have shown that malnutrition of the mother is associated with anencephaly and they conclude that low standards of nutrition may well be an ætiological factor in this condition—a conclusion which accords well with the careful clinical studies in Boston of Stuart, Burke, and their associates [7–10] Coffey and Jessop in their latest paper have therefore reported the effect of an epidemic of influenza on a population whose standards of nutrition are low—in an earlier control group of 192 mothers

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1 Turner, R , Lowther, C *Lancet*, 1960, i, 381
2 Evanson, J M , Sears, H T N *ibid* p 544
3 Lowe, R D , Rosenheim M L *ibid* p 655
4 Fowler, P B S *ibid* p 708
5 Turner, R., Lowther C *ibid* p 769
6 Dollery, C T , Emslie-Smith, D , McMichael J *ibid* p 296
7 Somers, K , Gitau, G R *S Afr med J* 1959, 33, 515
8 Somers, K , Gitau, G R. In preparation

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1 *Lancet*, 1959, ii, 935
2 Walker, W M , McKee, A P *Obst Gynec* 1959, 13, 394
3 Wilson, M G , Heins, H L , Imagawa, D T , Adams, J M *J Amer med Ass* 1959, 171, 638
4 Coffey, V P , Jessop, W J E *Irish J med Sci* 1955, 6 30
5 Coffey, V P , Jessop, W J E *Brit J prev soc Med* 1957, 11, 174
6 Coffey, V P , Jessop, W J E *Irish J med Sci* 1958, 6 391
7 Burke, B S , Beal, V A , Kirkwood, S B , Stuart, H C *J Nutr* 1943, 26, 569
8 Burke, B S , Harding, V V Stuart, H C *J Pediat* 1943, 23, 506
9 Burke, B S , Stuart, H C *J Amer med Ass* 1948, 137, 119
10 Burke, B S Stevenson, S S , Worcester J , Stuart, H C. *J Nutr* 1949, 38, 453

who had given birth to normal infants the total plasma-proteins were less than 5 5 g in 28 4% of women, and the hæmoglobin under 70% in 24 5% of women [5] Nothing is published of the living standards of the two groups of American mothers,[2] [3] but it would be surprising if they were as low as those in the Dublin study

Instead of suggesting that because the findings of the Dublin and American studies do not agree, one of them is *wrong*, Dr Trimble might perhaps have considered whether Asian influenza is more likely to increase the incidence of congenital abnormalities in a poor underfed population than in a more prosperous one—and if so, why?

London School of Hygiene
and Tropical Medicine,
London, W C 1

ROY M ACHESON

EXPIRED-AIR RESUSCITATION

SIR,—The report by Professor Woolmer and his colleagues (April 2) confirms the work that has been reported regarding the efficacy of an oral airway for performing direct artificial respiration (expired-air resuscitation)

It is not surprising that the untrained “ rescuers ” who performed resuscitation in the experiments described in your leading article had no difficulty in inserting a full-size anæsthetic-type airway, because their subjects were fully anæsthetised and paralysed for a surgical operation However, such conditions do not usually exist in the field, and the casual rescuer may well have difficulty in his attempts to insert such an airway Precious time may be lost if the jaw is tight, and even if the rescuer succeeds in placing the airway in the mouth, it might provoke retching and vomiting in a victim who may not be depressed to the level of unconsciousness where such reactions are abolished

For these reasons, it is still essential to teach the casual rescuer, as well as professional first-aiders, the essentials of *mouth-to-mouth and mouth-to-nose resuscitation—even if a* manikin must be resorted to in order to avoid æsthetic objections during training For those who are trained in resuscitation procedures, and for the casual rescuer who may need an airway (and who receives special training), I feel that the Brook airway (which has a shortened mouthpiece) fills the need best it is relatively easy to insert, it provides a satisfactory air-passage, and it will not provoke retching or vomiting in a semiconscious victim, and the one moving part is a siliconed one-way valve which has an “ infinite ” shelf life With the training programme previously described, most people can be taught this method of direct artificial respiration, which is highly efficient [1–3]

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ALLEN B DOBKIN

A PRACTICAL OXYHÆMOGLOBIN STANDARD

SIR,—Dr Stallybrass (April 16) is right to remind us that the present-day international standard hæmoglobin corresponds to 14 6 g per 100 ml The difficulty however in day-to-day hæmoglobinometry is the lack of a practical standard solution by which to measure samples With the almost universal use of oxyhæmoglobin in routine work, no adequate stable standard exists The grey solutions sometimes used *do not have the same absorption properties* as oxyhæmoglobin and conditions may occur in which a grey solution produces a constant reading in a photoelectric colorimeter while a solution of oxyhæmoglobin will vary considerably

An important contribution to this problem was made when Prof E J King and Dr I D P Wootton, of the Postgraduate Medical School, undertook to provide laboratories at monthly intervals with a blood specimen chemically standardised for hæmoglobin content This ensured that at least once a month it was possible to check the accuracy of our hæmoglobinometry The demand for this valuable service has grown, and distribution of the specimens was later undertaken by Messrs D C Keeler The difficulty remains however that variations in apparatus occur unexpectedly, and in the absence of a reliable standard it may be some time before deviations are detected.

For the past year I have used a solution of hæmoglobin in 50% (v/v) glycerol as a standard When checked at monthly intervals against the chemically standardised specimen supplied by Messrs Keeler, it has proved remarkably constant, and no variation in its absorption spectrum has been observed in this time Two strengths of hæmoglobin solution are made to correspond to about 14 g and 7 g per 100 ml, when read in the apparatus in use A fresh blood specimen is lysed in 0 04% ammonia, and an equal volume of glycerol is added and thoroughly mixed These stock solutions are kept at about −20°C and are removed from the refrigerator only to take a sample The freezing-point of the solution is well below this temperature For every day use it is found convenient to keep samples of these solutions in standard cells or test-tubes normally used, and again these are returned to the refrigerator as soon as their readings have been checked These solutions should not be left at room temperature for any length of time.

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London, W 9

J FIELDING

RESISTANT TUBERCLE BACILLI

SIR,—Your leading article of March 12 on the subject of primary bacterial resistance is timely

In Ghana, we have investigated the extent and pattern of bacterial resistance in 448 previously untreated cases of symptomatic pulmonary tuberculosis reporting for treatment at one centre in Ashanti during the period May to December, 1958, and have demonstrated resistance to streptomycin in 9 1%, to P A S in 5 2%, and to isoniazid in 8 2% Around 10% were resistant to one drug only and some 4 5% to two or three drugs These figures represent a gross rise of 10% over the estimated level for 1957 The levels of resistance among new cases reporting for treatment and admitting previous chemotherapy elsewhere were 37 6% resistant to streptomycin, 28 6% to isoniazid, and 5 0% to P A S—resistance to two or three drugs being demonstrated in almost all resistant cases

Chemotherapy, applied in the definitive sense, is known to be effective in the treatment of pulmonary tuberculosis provided drugs are applied in adequate dosage, in suitable combination, with constancy, and over a sufficiently prolonged period of time The Tuberculosis Chemotherapy Centre, Madras, has laid down the minimum requirements for the success of domiciliary chemotherapy in a tropical urban centre, but almost none of these is available over wide areas of tropical Africa The resistance figures for East and West Africa particularly underline what is likely to happen when definitive chemotherapy is applied under existing field conditions in underdeveloped territories In Ashanti (and conditions there are similar to those in most other parts of West Africa) it is necessary to apply chemotherapy in the definitive sense, and it must be entirely ambulatory in the majority At a practical level, therefore, the active treatment of pulmonary tuberculosis generally rests in the application of combinations of P A S and isoniazid which, *in view of the scattered nature of the population*, must be taken without supervision Recent work in West Africa has demonstrated that many do not take P A S regularly (whether P A S be dispensed separately from isoniazid or in the form of combined pills or cachets) and that the majority abscond during an early stage in treatment Under conditions such as these, and considering that disease is usually extensive and often heavily cavitated, it is not surprising that high levels of bacterial resistance exist It is certain that they will increase in the future as rapidly as they have in the

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1 Dobkin, A B *Lancet*, 1959, ii, 662
2 Dobkin, A B *Canad med Ass J* 1959, 81, 458
3 Brook, M , Brook, J *ibid* 1960, 82, 245

past unless urgent measures are introduced to rationalise management of the disease.

On the other hand, the matter of the clinical significance of bacterial resistance requires full investigation. Preferably such research as is required should be undertaken in Africa where the incidence of disease is high and where, from the available evidence, the resistance problem is most acute.

W. J. BELL
P. P. BROWN
West African Council for Medical Research,
Tuberculosis Research Unit, Accra.

THE PERSONAL DOCTOR

SIR,—Dr Fox's review of medical care in the United States (April 2) has afforded me many insights. I find most of his argument on the functions of the personal doctor highly acceptable except in one respect: the health centre appears to me to provide some of the things necessary for the personal doctor's survival.

Dr Fox mentions three ways in which health centres may contradict the ideal pursuit of personal doctoring.

(*a*) A specially designed building may detract from the homely relationship between doctor and patient.

(*b*) The use of ancillary workers (social workers, technicians, clerks, nurses) may interfere with the relationship between doctor and patient.

(*c*) Group facilities provide "heavy arms" for what should be a light mobile force in the battle for health.

But to deny the practitioner discussion with colleagues in general practice, adequate consulting-rooms, equipment, and ancillary help is perhaps to send him out altogether unarmed, and to deprive him of much that medical science has to offer. He surely needs to extend his diagnostic potential and to be economical with his time.

These requirements Dr Fox implicitly concedes, and they seem to me to demand a centre. But he considers them less important than the personal relationship with which they may interfere. Yet he points out that "some doctors could make their patients feel like personal friends if they received them inside a refrigerator". Extremes make good arguments, and this observation tells us that the quality of the personal relationship depends on something other than buildings and equipment. The extreme of this personal relationship is institutionalised in psychoanalysis, a case in which it is independent of such factors. Furthermore, many doctors working in association with each other or with social workers and nurses will testify that such groupings do not necessarily destroy the personal relationship. But it is certainly true that the increasing and inevitable specialisation in medicine is inimical to this relationship, except for the psychotherapist whose specialty it is.

The root of the personal relationship lies in the nature of the authority and responsibility which the doctor assumes with his patient (a conclusion which I must acknowledge I have reached by following through Dr Fox's own arguments on professional freedom).

This responsibility is enshrined in the professional ethos of medicine, a set of rules essential to medical practice before the advent of technology in medicine. Without effective remedies, the doctor was obliged to rely for therapy largely on his interpretation of the natural history of an illness and the accommodation of this interpretation to the patient's psychological needs. He had to obtain a reliable history of symptoms, and complete confidence was necessary if the patient was to yield to anyone such intimate access to his life and body, and such extra-ordinary power over him. This was achieved through the set of rules embodied in the Hippocratic Oath. The obverse of this voluntary submission by the patient was the acceptance by the doctor of authority and full responsibility for the patient. Today some specialties may appear to have less need of this ethos, because attention is confined to a technical and restricted aspect of the patient's illness, and the social and psychological context of the illness can be ignored; in such a case responsibility usually rests elsewhere, depending on the particular organisation. This I think is part of the explanation for the lack of personal doctoring in specialties.

A main function of general practice is to maintain this traditional professional relationship—in other words, to offer the patient a single practitioner who will undertake full and continuing responsibility for him.

Such responsibility encourages the doctor to extend the boundary of medical care to whatever may concern the patient's health, and this therefore includes the social and psychological matrix of illness. Indeed, as Dr Fox is concerned to show, the value of the professional relationship is largely in the psychological and social support which it offers the patient together with physical care—a combination which the patient can expect only from a practitioner who takes full responsibility for him in the traditional professional sense.

Dr Fox shows that in the U.S.A. the basis of this personal relationship is being lost to medical practice. This is because with specialisation and large organisations goes a tendency to divided responsibility, the delegation of authority, and a chain of command. The doctor in the Family Health Demonstration at Montefiore delegates his authority in psychological and social matters to the psychiatric social worker and the health visitor and works in a *democratic* team. Once he does this he no longer has full responsibility, and the conditions for the full development of the personal relationship no longer exist.

For the practitioner to accept full and continuous professional responsibility (with the hospital as a specialist supporting service), he requires not only general clinical competence but competence in the social and psychological aspects of practice, so that the needs of the patient in his social context can be met. The home and family have to be seen, studied, and understood; and, if the practitioner is to hold this traditional area of medical practice, he will have to apply what psychology and sociology can teach to the so-called art of medicine.

To achieve psychological and social insights it is an advantage, even a necessity, to take the family as the basic unit of practice. Social and family problems cannot easily be brought into the scope of domiciliary care without the collaboration of medicosocial workers and home nurses. In addition, his function as family doctor would need to include the care of children, which in Britain is often the province of the clinic doctor, if not, as in the U.S.A., of the pædiatrician. This would be not only a step towards family practice, but one step towards achieving that unity of promotive, preventive, and curative work necessary to clinical competence. To incorporate into routine work preventive health examinations, screening techniques, and the maintenance of the chronic ambulant patient, modern clinical methods and technicians would be needed.

Thus in order to care for the whole family, in sickness and in health, the personal doctor would best take over and develop the personal services now given by local authorities, and he would have to be helped in this work by their ancillary workers. He would be the *leader* of a domiciliary team based on his practice. It seems to me that these are the minimal requirements which would enable the modern doctor to exercise the full and undivided professional responsibility that is fundamental to a personal relationship between doctor and patient.

Without these he risks becoming a psychotherapist or social worker of the second rank. Alternatively medical practice could abrogate this field and leave it to lay healers and priests, or psychologists and social workers, which latter is the implied solution of the Family Health Demonstration.

The development I have outlined could not take place without the kind of group organisation for which a health centre is designed. It would be uneconomical not to share these facilities.

It seems to me also that the view that the patient wants to attend a surgery that looks as much like a home as possible may be a projection, or an idealisation, of the 19th-century family doctor with a middle-class practice. But even if it is important, architectural guile is sufficient to solve this problem, as I think is well demonstrated in the Darbishire House Health Centre of Manchester University. To my eye, this looks more like a modest home than many private houses in some modern cities.

My argument, then, is that to achieve a personal relationship between doctor and patient, the crucial point is the distribution of professional authority and the form of administrative organisation. On this view the health centre is not a halfway house between specialist and personal doctor, it is an arrangement which allows the personal doctor to develop his utmost skill.

Department of Social
and Preventive Medicine,
University of Manchester

MERVYN SUSSER.

SIR,—There can be no doubt that personal practice (ex general practice) is the most important and most difficult specialty in medicine. Are we satisfied that the medical schools are giving as much attention to training in this specialty as they give to others? Can it be done without bringing some general practitioners into the hospital—for example, in charge of the casualty department?

One of your contributors suggests that *time* should only be spent on a patient when he is "really sick" and not when he or she is "bellyaching", which presumably is a mental condition and not an abdominal one. Is it not the duty of any practitioner to try to cure the patient of this mental condition, which may in some cases be as crippling as a physical disease, instead of "speedily dismissing" him or her?

In my work I sometimes meet these "bellyachers" and hear their moans about their doctors. When talking to them I always try to be loyal to the profession, but in some cases there does seem to have been a "slip-up" on the part of the overworked doctor.

Oxford

MALCOLM DONALDSON.

HYPNOSIS AND UNREGISTERED PRACTITIONERS

MR PETER CASSON writes:

"Dr Mason (Feb 13) asks for information concerning harm done by hypnotists. His task is that of ' investigating the problem of *lay hypnotists* and the possible harmful effects which can be caused by the use of hypnosis by *unqualified practitioners* great assistance to have available all the details of harmful effects which have followed the use of hypnosis by *unregistered practitioners* of patients suffering from harm following the use of hypnosis by *unqualified practitioners* ' (my italics). Surely the investigation would be more scientifically oriented if Dr Mason were to ask for information regarding anything adverse caused by *any* individuals using hypnosis? There is *no* 'qualification' in hypnotism, either lay or medical, other than diplomas issued by various self-inaugurated societies, but this as a 'qualification' is rather a homemade affair.

"Hypnotism is a psychological subject, not a medical one. Many of the major works on hypnosis are written by non medically-qualified psychologists. The major research on hypnosis in this country is being carried out by non-medically qualified psychologists. To me, Dr Mason's proposal shows irrational bias, and I believe that his search will be unproductive.

"I, too, should be very interested to receive information about alleged harm done by hypnotism and I am sure that the fairmindedness of your readers would permit them to send me (at 17, Dorset Square, London, N.W.1) a copy of any information they send to Dr Mason, for I am concerned with the correct application of hypnosis to medical and psychological problems.

"Please do not assume from the foregoing that I am anti-medical, far from it my best friends are doctors and psychiatrists, I have trained quite a number in hypnosis, and all my patients with psychosomatic symptoms are vetted by their doctors before I treat them."

Obituary

HALLIDAY GIBSON SUTHERLAND

M.D. Edin.

DR HALLIDAY SUTHERLAND, who died in London on April 19 at the age of 77, was a versatile man. His experience, both inside and outside medicine, was varied and unusual, and with his natural talent for writing he used it to good effect in his reminiscences and in his books on social medicine.

The eldest son of Dr J. F. Sutherland, a member of the Board of Control for Scotland, he was educated at Glasgow High School and Merchiston Castle School. After qualifying from the University of Edinburgh in 1906 he became an assistant in his uncle's practice in Spain, with some bullfighting as a hazardous hobby. At Edinburgh, Sir Robert Philip had already aroused Sutherland's interest in diseases of the chest, and soon after his return to this country he became medical superintendent of the Westmoreland Sanatorium and later medical officer at the Marylebone tuberculosis dispensary. During the 1914–18 war he served as a temporary surgeon lieutenant in an armed merchant cruiser, and in the Royal Air Force. After the war he spent some fifteen years in general practice in Islington and later in Kensington, but he retained his interest in chest disease and also held part-time posts in that specialty.

Soon after the late war began he was appointed an assistant M.O.H. at Coventry and later he joined the mass-radiography centre at Birmingham, becoming director in 1948. He retired in 1951.

Throughout this full and active life he had found time for travelling and writing. One of his first books on his specialty was the *Control and Eradication of Tuberculosis*, which appeared in 1912. The *Arches of the Years*, published in 1933, described his life to the end of the 1914–18 war. Other books described journeys in Lapland, Scotland, Spain, and Ireland, and a lecture tour in Australia.

L. F. writes:

"Ever since his school and undergraduate days Sutherland had shown conspicuous literary ability, and it was no surprise to his friends that he achieved his major successes as an author. Blessed with a forceful personality, a puckish wit, and an insatiable appetite for adventure, he had also the rarer gift of communicating these qualities to paper. All his books contained entertaining material though none ever rivalled the first two picturesque autobiographies (*The Arches of the Years* and *A Time to Keep*). Halliday claimed to have been one of the few Englishmen, and probably the only member of the British Medical Association, to have played a bull in a

Spanish arena, and no-one who knew him could doubt it His most bloodcurdling adventure, however, was in the 1914–18 war when, on reporting aboard ship, he was confronted by a worried first lieutenant who peremptorily instructed him to certify the captain insane, as he was giving orders which would sink the ship Mimicry was one of Halliday's striking gifts and he was particularly admired for his uncanny skill in reproducing the foibles of his chief, Sir Robert Philip It was sheer bad luck that his richest performance was given over the telephone, not as he thought to a fellow house-officer, but to the highly amused Sir Robert himself who loved to recite the story later

"Controversy in speech and writing was the breath of Sutherland's life He was eloquent and sincere but his perfervid Celtic spirit often impelled him far beyond his belief After his conversion to the Catholic Church he devoted immense energy to upholding its medico-moral code, especially the prohibition of contraceptives In his professional work he remained a devoted ally to Sir Robert Philip and rendered fine service in many departments of the great campaign against tuberculosis"

Dr Sutherland married in 1920 Muriel, daughter of J F Fitzpatrick. They had one daughter and five sons, one of whom was killed in the late war

Sir ARCHIBALD McINDOE

P H M-B writes

"While supporting the tributes to the wonderful work which Archibald McIndoe has performed for plastic surgery and to his service for humanity, may I, as one of his former colleagues at the Hospital for Tropical Diseases, point out that he was elected surgeon to this hospital, then in Endsleigh Gardens, in 1932, and lecturer in tropical surgery at the London School of Hygiene and Tropical Medicine, posts which he held till 1939 These facts have escaped notice in his obituaries, yet it was here that he obtained an entry to surgical London, and facilities for beginning his work in plastic surgery"

Parliament

Limb-fitting Centres

In the course of an adjournment debate on April 14 on the work of the British Limbless Ex-Servicemen's Association, Sir ROBERT CARY asked whether the work done at Roehampton could be decentralised by the creation of area limb-centres attached to the main orthopædic hospitals

In her reply Miss EDITH PITT, parliamentary secretary to the Ministry of Health, said that a large artificial-limb and appliance centre needed about 20,000 sq ft. and costs £100,000 to build. Centres had to be near bus stops, and there had to be plenty of space for ambulances and for testing patients on tricycles Most of the Ministry of Pensions limb-centres started as part of its regional offices, and, except at Roehampton and Leeds, were originally office accommodation. The Ministry wanted to have them in hospitals, but as there were 21 centres of different sizes in England and Wales which did limb-fittings (and 9 others which did not) it would be costly to get them all in the right place—beside a hospital with an orthopædic department. They had to fit in with general hospital planning, and it was difficult to find really good sites for this specialised purpose. But where a centre had to be moved because it was inadequate they hoped in future to site it in or beside a hospital conveniently situated for the limbless which had an orthopædic department. A year or two ago the Wolverhampton centre had been moved to the New Cross Hospital In Liverpool, they hoped to start building very soon at Mill Road Hospital, in Birmingham at Selly Oak Hospital, in Leicester at Leicester Royal Infirmary, and in Portsmouth at St Mary's Hospital. Though they had not brought the limb service within the National Health Service, their aim was to bring the centres and the hospitals closer together

Diary of the Week

MAY 1 TO 7

Monday, 2nd

Royal College of Surgeons of England, Lincoln s Inn Fields, W C.2
5 P.M. Prof P K Duraiswami Experimental Causation of Congenital Defects (Hunterian lecture.)
University of London
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W C.1) Prof A A. Liebow (Connecticut) Birth and Growth of Collateral Vessels
Postgraduate Medical School of London, *Ducane Road*, W 12
4 P.M. Dr L. R. West Echinococcosis
Wright-Fleming Institute of Microbiology, St. Mary's Hospital W.2
5 P.M. Prof A St. G Huggett Fœtus as an Anaerobe—Some Prenatal Problems (Almroth Wright lecture.)
University of Birmingham, Birmingham, 15
5 P.M Prof J Z. Young Mechanisms of Learning and Form Discrimination. (First of three William Withering lectures)

Tuesday, 3rd

Royal College of Surgeons of England
5 P.M Dr J R. B Williams Polymyositis
University of London
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Prof E Husted (Copenhagen) Ameloblastoma.
St Mary's Hospital Medical School, Paddington, W.2
5 P.M. Prof J K. Russell Megaloblastic Anæmia of Pregnancy
Institute of Dermatology, Lisle Street, W C.2
5.30 P.M Dr H. J Wallace Vascular Anomalies in the Lower Limbs
Institute of Neurology, The National Hospital, Queen Square, W C.1
5.30 P.M Prof K. J Zülch (Cologne) Recent Work on Cerebral and Spinal Infarction.
University of Birmingham
9 P.M. Professor Young Mechanisms of Learning and Form Discrimination. (Second of three William Withering lectures)

Wednesday, 4th

Royal Society of Medicine, 1, Wimpole Street, W 1
5 15 P.M *History of Medicine* Dr Cuthbert Dukes London Medical Societies in the 18th Century (Presidential address.)
8 P.M. *Surgery* Mr D H Patey, Mr L. P Le Quesne, Dr C. G Whiteside, Prof A. G R. Lowdon Cholangiography
Royal Free Hospital, Gray's Inn Road, W C.1
5 15 P.M. Dr W W McDermott, Jr (Boston) Hepatic Coma.
Postgraduate Medical School of London
2 P.M. Dr R. E. B Hudson The Human Pacemaker and its Pathology
Institute of Dermatology
5.30 P.M. Dr R. W Riddell Fungi as Saprophytes and Pathogens
Institute of Diseases of the Chest, Brompton, S W.3
5 P.M. Dr N C. Oswald Pulmonary Changes in the Reticuloses
Assurance Medical Society
5 P.M. (11, Chandos Street, W 1) Dr F Avery Jones Prognosis in Alimentary Disease
University of Birmingham
5 P.M. Professor Young Mechanisms of Learning and Form Discrimination. (Last of three William Withering lectures)
Medico-Chirurgical Society of Edinburgh
8.30 P.M (18, Nicolson Street, Edinburgh.) Prof G W A. Dick Poliomyelitis

Thursday, 5th

Royal College of Surgeons of England
5.30 P.M. Sir Victor Negus Air Conditioning in the Nose.
Royal Society of Medicine
8 P.M *Neurology* Dr W H. McMenemey, Dr Macdonald Critchley History of Neurology
Postgraduate Medical School of London
4 P.M. Dr H T Howat Diagnosis and Treatment of Pancreatic Disease.
Honyman Gillespie Lecture
5 P.M. (University New Buildings Teviot Place, Edinburgh.) Prof P R. Allison Swallowing and Dysphagia.
University of St Andrews
5 P.M (Queen s College, Dundee.) Prof T Ferguson Rodger The Neuropharmacological Approach to Psychiatry
University of Aberdeen
5 P.M. (Medical School, Foresterhill.) Prof R. B Welbourn Hypophysectomy in Advanced Breast Cancer

Friday, 6th

Royal Society of Medicine
10.30 A.M *Otology* Dr A. Glorig (Los Angeles) Air Marshal E. D D Dickson, Dr Donald Stewart Effects of Noise Upon Hearing
3.20 P.M *Laryngology* Mr H D Brown Kelly Dysphagia in Adults (non-malignant), its Diagnosis and Management. Prof Truls Leegard (Oslo) Management of Chemical Burns of the Œsophagus
5.30 P.M. *Anæsthetics* Mr W D Tavernor Anæsthetic Procedures in the Larger Domesticated Animals
Postgraduate Medical School of London
10 A.M Dr Deborah Doniach Ancillary Diagnostic Methods in Thyroid Disease.
Institute of Neurology
4.30 P.M. Dr J Purdon Martin Observations on Muscular Rigidity and Its Relation to the Functions of the Basal Ganglia.
Royal College of Surgeons of Edinburgh Edinburgh, 8
3.30 P.M Dr A. Rae Gilchrist The Cardiac Patient as a Surgical Problem.

Saturday, 7th

Royal College of Surgeons of England, Faculty of Anæsthetists
10.30 A.M. Prof E. A. Pask, Squadron-Leader J Ernsting, Dr J B Brierley, Dr P D Bedford, Dr B R. J Simpson Hypoxia.
Institute of Laryngology and Otology, 330, Gray's Inn Road, W C 1
NOON Prof S Podvinic (Belgrade) Upper Respiratory Pathology in Asthma.

Notes and News

FREE MEDICAL CARE FOR THE ELDERLY IN THE UNITED STATES ?

FROM A CORRESPONDENT IN NEW YORK

ONE of the key issues in the developing Presidential campaign is the Forand Bill, which would provide free hospital and other medical care for Social Security pensioners More mail is now pouring into Washington on this subject than on any other legislative proposal, and both physicians and laymen are conducting pro and con campaigns which will have far-reaching effects on both national and State political campaigns

The Bill, originally introduced in 1957 by Representative Aime J Forand, a Democrat of Rhode Island, would provide up to 60 days' hospital care, 120 " nursing-home " care, and payment of surgical bills for Social Security pensioners aged 65 and over It would be paid for by increasing the Social Security tax by $^{1}/_{2}$%, with employer and employee paying a quarter each With a rapidly increasing older population—now estimated as being over 15,000,000 in the 65-and-older category—the Bill has won tremendous support among the elderly and from many labour unions On the other hand, it is being strongly opposed by organised medicine

In a curious development, a plan advanced by Secretary of Health, Education, and Welfare Arthur S Flemming was turned down by President Eisenhower Flemming's plan was a subsidised system of voluntary health insurance for the aged The Flemming plan encompassed private companies providing insurance covering the cost of hospital and nursing-home care, with the Federal Government sharing the major costs of the insurance premiums Such insurance would be available to citizens at the age of 65 who had incomes of less than $4000

Mr Flemming was, in effect, left hanging on a limb So were various Republican Party officials who realise how crucial the issue will be in the Fall elections While Vice-President Richard Nixon, leading Republican Presidential candidate, is supposedly aligned with the Administration in opposition to the compulsory aspects of any insurance plan for the aged, Nixon is expected to come forward with an alternative plan in the near future

Meanwhile, both the American Medical Association and the American Academy of General Practice are waging intensive war against the Forand Bill, while labour unions rally to support it The battle is being fought in a setting in which voluntary health-insurance plans are in ferment throughout the country The sharply rising costs of hospital care and drugs have impelled many Blue Cross groups, voluntary health-insurance plans, to ask for large increases in what their subscribers pay These applications for higher rates have, in turn, caused many labour unions to protest and to threaten to set up their own health-insurance plans Such threats have been raised both in New York City and in Detroit, while Blue Cross leaders have moved in the direction of one national Blue Cross organisation

Illustrative of the heat of this controversy was a union rally of 6000 retired trade unionists in New York City to support the Forand Bill, in which President Eisenhower was sharply criticised for his opposition to the measure Another sign of the keen feeling was the recent meeting in Philadelphia of the American Academy of General Practice, which urged its 26,000 physician members to send postcards and telegrams to Washington against the Bill

MENTAL NURSING

ALMOST every paper that has been written about the changes that are being made in the care of mental patients show, either explicitly or implicitly, how much depends on the nurses Not only are there more nurses than doctors, but nurses spend more time with each patient In practice the patient must therefore depend on the nurse for much of the support and stimulus which help him to return to the community By virtue of their own numbers and of the hours they work, the nurses are bound also to have an important influence on the atmosphere of the " therapeutic community " which is now part of the patient's active treatment A committee of the Royal College of Nursing have been considering how the ward sister and charge nurse can meet these new responsibilities and opportunities[1]

Many of their recommendations seek to ensure that the mental nurse should be consulted more freely, and kept more fully informed about policy in her own hospital, and that she should be represented on the nursing committees of the areas and regions Another group of recommendations is concerned with opportunities for study and research Promotion to ward sister and charge nurse should depend on willingness and ability to teach, and there should be a close link between classroom teaching and ward practice The possibility of a shortened combined training for mental and mental-deficiency nurses is suggested On the controversial question of an entrance examination to training the committee support an obligatory selection test

Research in the care of long-stay patients and a critical review of traditional equipment and practice are other suggestions that will enable the nurse to find more satisfaction in her work and more time and energy to give her patients the modern treatment which so largely depends on old-fashioned kindness and sympathy

HOSPITAL PLANS FOR WESSEX

ONLY a year after achieving full independence, the Wessex Regional Hospital Board last week gave a remarkably full account of how it means to develop its hospitals between now and 1972[2] Having no medical school or teaching hospital within its boundaries, it has to provide some services which elsewhere are the responsibility of two separate boards

Mr S V Christie-Miller, chairman of the finance committee, estimates from Government statements that in this period a total of £532 million is likely to be available for hospital development in England and Wales, and he thinks that the Wessex board, with nearly 2 million people to look after, can hope for £24 million, of which £7 million may come out of its normal allocation while £17 million will go to schemes financed centrally by the Minister Already it has had sanction for centrally financed schemes costing nearly £4 million If the nation cannot live up to its economic expectations, the programme will remain the same but will take longer to complete, while if the Government are able to step up their capital investment in hospitals the work can be done sooner The cost of the hospital service has come in for criticism in recent months, but " modern buildings mean less upkeep, lower costs, and better standards "

Mr P G Templeman, the chairman, spoke more specifically of delays in outpatient departments (caused by shortages of space and makeshift arrangements), the risks of sepsis, the obstacles to modern nursing and treatment, and the shortage of beds for mental defectives The region has 115 hospitals with 17,400 beds, and the capital expenditure since 1948 has nearly all been on short-term remedies Among the board's major aims, described by Prof J E G Raymont, chairman of the planning committee, are

1 That each general hospital group should have an adequate main accident, orthopædic, casualty, and outpatient hospital

2 That each outpatient hospital should have its supporting inpatient beds

3 That each community should have a psychiatric outpatient clinic, short-stay unit, and day hospital within easy reach, and adequate medium-stay rehabilitation facilities " We want to see our Mental Health services closely integrated with local health authority services, adequate occupational therapy buildings, and last, but by no means least, an end to overcrowding on the wards "

Standards in operating-theatres are to be improved, and sterile articles are to be supplied to all hospitals from central sources As chairman of the medical advisory committee, Mr H H Langston also drew special attention to " the major emergency presented by the present-day accident", and the special problem of the ever-increasing accidents on the roads running through the Wessex region to the south and south-west

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[1] A Comprehensive Mental Nursing Service—the Part of the Ward Sister and Charge Nurse 1960 Obtainable from the college, 1a, Henrietta Place, London, W 1 Pp 33 2*s* 6*d*

[2] Documents presented at a press conference on April 13 The board's address is Highcroft, Romsey Road, Winchester

The board's plans take the form of 17 major projects, which are set out with a timetable for their completion

IMPERIAL CANCER RESEARCH FUND

THE Fund's new laboratories, now being built on the site of 44–46, Lincoln's Inn Fields, should be completed by the middle of next year They are to cost at least a million pounds with another quarter of a million for their equipment, and the hon treasurer's report, presented to the annual meeting on April 21, says that at least half a million pounds a year will be needed to maintain these buildings and the expanding team of scientific workers Last year's expenditure was about £200,000

In preparation for the expansion and reorganisation, ten new members of the staff have been appointed, and last October Dr G F Marrian assumed full-time duties as director of research The main subjects of investigation at Mill Hill and at Lincoln's Inn Fields are (1) the tumour-inducing properties of viruses, (2) the endocrinological aspects of cancer, (3) the leukæmias, and (4) the biological properties of tumour cells At present the two first are absorbing the greater part of the research manpower, and one of the events of the year was the isolation by Dr G Negroni (from an Ak mouse with spontaneous leukæmia) of an agent resembling the polyoma virus studied by Gross, Stewart, and others in the United States The report (obtainable from the Fund's office at the Royal College of Surgeons, Lincoln's Inn Fields, London, W C.2) reproduces a remarkable electron photograph of a particle of this virus magnified 960,000 times

A NEW INSTITUTE OF COMPARATIVE MEDICINE

THE Nuffield Foundation has made a grant of £100,000 to the Zoological Society of London to found an institute of comparative medicine, and to provide two senior research fellowships The council of the society has asked that the name of Lord Nuffield should be associated with the name of the institute

The society already has a modern animal hospital, and the institute will offer opportunity to increase knowledge of disease in animals, and thus serve the health of the society's collections A committee of medical and veterinary specialists under the chairmanship of Sir Roy Cameron, with a planning group under the chairmanship of Prof G Payling Wright, has been appointed to advise the council on the organisation of the institute

Mr Richard Llewelyn Davies, director of the Nuffield Foundation division for architectural studies and professor elect of architecture in the University of London, will design the new building in accord with the overall plan for the gardens that has been devised by Sir Hugh Casson in collaboration with Mr F A Stengelhofen, the society's resident architect It is hoped that, in planning the institute, effect can be given to conclusions drawn from the study of laboratory designs for which the Foundation has been responsible over the past few years

ILLNESS FROM COTTON DUST

BYSSINOSIS is still a serious problem in the Lancashire cotton industry Dr R S F Schilling, who gave the Milroy lectures on this subject in 1956,[1] addressed the section of general practice of the Manchester Medical Society on March 28, when he said that in 1957–58, out of some 50,000 at risk, 68 cotton workers were recorded as dying of byssinosis and 448 received disability pensions Investigations are in progress in this country, in Germany, and in Holland to discover the pharmacologically active constituent in the cotton dust causing the characteristic symptoms of chest tightness As the immediate need is to reduce the dust a combined clinical and environmental study has been made in Lancashire cotton mills[2] to determine safe levels of dust concentraton At concentrations of less than 100 mg per 100 cubic metres, no workers had symptoms of byssinosis, but at present it is not possible to achieve this level of dust control The Shirley Device, which is a local exhaust ventilation system applied to the dusty points of a carding-engine, substantially reduces dust concentrations, and there is reason to hope that even in the dustiest mills concentrations of less than 250 mg per c m can be achieved This is the immediate target for dust suppression recommended to the industry At concentrations between 100 and 250 mg per c m, 17 out of 250 workers at risk had persistent symptoms of byssinosis Cardroom workers should therefore have regular medical examinations, so that those who are susceptible can be advised to leave their dusty environment before they are permanently disabled

NEW AMŒBICIDES

CLINICAL trials with some new synthetic amœbicides, which have been undertaken in the medical unit of the Hospital for Tropical Diseases, London, were reported last week by Dr Stanley Bell, in a paper given to the Royal Society of Tropical Medicine and Hygiene

The therapeutic efficacy of 'Entamide' (diloxanide) has previously been described, and the three new salts recently assessed are diloxanide benzoate, diloxanide piperazine sulphate, and diloxanide furoate. Of these the furoate has proved outstandingly successful, having an in-vitro activity 100 times as great as its parent substance diloxanide. The other salts are now principally of interest because of their differing absorbability from the gut while having similar in-vitro activity The more absorbable piperazine sulphate has to date proved slightly more effective than the less absorbable benzoate

Complementing the trials carried out in London, trials have been carried out in Nigeria by Dr P D Marsden on the unit staff, and in these the efficacy of the furoate salt has been fully confirmed.

EXPIRED-AIR RESUSCITATION

As mentioned in our leading article of April 2, films have been made for showing first-aiders how to use the airways now recommended for direct artificial respiration Dr Allen B Dobkin, of the University of Saskatchewan, whose paper on training with the Brook airway appeared last October (*Lancet*, 1959, ii, 662) tells us that the film *That They May Live*, and other training aids, can be seen by doctors in this country on application to Mr C N Turner, Smith & Nephew Ltd, Welwyn Garden City, Herts By arrangement with the University of Saskatchewan and Dr M Brook, the aids are obtainable from the Safety Supply Company of Toronto The Brook airway is supplied in this country by W H Bailey & Sons, Ltd, 80, Bessborough Place, London, S W 1 For copies of the film, application should be made to Dr A B Dobkin, Department of Anæsthesia, University of Saskatchewan, Saskatoon, Canada

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University of Leeds

On Wednesday, May 11, at 3 P M at the General Infirmary at Leeds, Sir Howard Florey will give the Matthew Stewart lecture He will speak on contributions of the electron microscope to the understanding of pathological processes

University of Edinburgh

Colonel J E C Robinson has been appointed part-time lecturer in the department of public health and social medicine

North Middlesex Hospital

On April 26 Princess Margaret opened a new outpatient department at this hospital

The department is housed in a four-storey block with a two-storey block on its north side The chest clinic is on the lower ground floor The patients' reception-room, records, appointment offices, urological department, five general-purpose clinics, dental treatment room and operating-theatre, outpatients' pharmacy, pathological laboratory, and X-ray department are on the ground floor The department of physical medicine, which is on the first floor, has a hydrotherapy pool, three treatment rooms, gymnasiums, consulting-rooms, and examination cubicles, and an electrically screened room for electromyograph equipment The main hospital pharmacy is on the first floor, together with a department for electrocardiography and clinical photography

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[1] Schilling R S F *Lancet*, 1956, ii, 261, 319

[2] Roach, S A., Schilling R S F *Brit J indust med*, 1960, 17, 1

Royal College of Surgeons of England

The following diplomas have been granted jointly with the Royal College of Physicians

D A—G K Stratford, R J B Thomson

D.L O—M W Brown

D P M—D H Miller

D I H—M C Narawane

D Phys.Med—E D R Campbell, Raymond Greenwood, P N Knight

D C H—Fadhil Khalil Abbousy, Israel Falke Abroms, Fadl Muhammed Abu-Laban, Soliman Husein Abu-Sittah, Patricia M Akers, Jassim Mohammed Ali Al-Jawad, Jayant Shivabhai Amin, Asuquo Udo Antia, Bimla Arora, Audrey M Ashworth, P G Atkinson, Jehangir Edalji Banatvala, Ivy Barua, Shirley A Batten, Phyllis J A Bell, V A W Blunt, J R F Boger, M D Bowie, K A C Brown, W D Bruce, W L Burland, Gwendolyn A Burt, D J C Cameron, Susan Campbell, Fook Kwee Chai, Tuck Kin Cham, Muthyala Chinna Pulliah Chetty, Gloria Cohen, Jean L Cooper, Anna Cope, Gerald Corney, D W Davies, Patricia W R Daymond, Lalitha A de Silva, Ponnahennedige Asoka Dias, Chandulal Sakerchand Doshi, A E J Evans, D R L Fernando, Elizabeth A Fisher, Jacoba Geefhuysen, Mohamad Iqbal Ghayur, Patricia A Girling, J H Goode, Bhola Nath Gupta, Margaret E Happold, Razia Hasan, Naghat Hashmi, Joan M C Henderson, B D Hewitt, Marion E Howard, Barbara H Hutchinson-Smith, David Jacobson, Kanaya Harchandrai Jagasia, Elizabeth R Jane, Mirza Agha Khan Javid, Cledwyn Watkin Jenkins, B F Johnson, R P Johnson, Shridhar Vinayak Joshi, J D Jowitt, Bishwa Nath Kapoor, H B Kean, Syed Usman Khaliq, J B Klaff, Parwati Shakuntala Limaye, Rhona Lindup, J M Littlewood, D H Livingston, Anne V C Lloyd, Shan-Shi Lo, Wan-Yee Lo, Tee Fun Loh, J E R Lorimer, Maureen T Lovett, Jane S McFarlane, J G McHugh, Jean L McNair, Ma Khin Ohn, Anne D Micah, Raymond Million, Gillian A Moody, Barbara A Moss, D S Munro, C H Nourse, D J O'Connell, Margaret E D O'Flynn, Margaret M R O Garra, Eileen T O'Halloran, Bridget O'Keeffe, Mohamed Osman, K R Parker, Babubhai Mathurbhai Patel, Alina T Piesowicz, Alice Shun-Haan Poon, Gwenllian J Pryce, Mohammed Amin Radi, J C L Rawes, David Redstone, J D Reid, M E Rivlin, G A Russell, Jayantilal Mohanlal Shah, Srinivasalu Naidu Shamanthakamani, Hafizulla Shariff, Mukteshwar Prasad Singh, Bishwambhar Dayal Sinha, R P Snaith, K G R Somer, Gillian Strube, Myrtle E Summerly, Anand Mohan Sur, Garden Hepburn Swapp, A R Taylor, Margaret Taylor, Marian A Taylor, Prija Thanasuwat, Edith H Thomas, Lesley F Thomas, Eunice V Turner, R L Walker, J R Wilson, I G Yule

D M R T—Shu-Chen Huang, Kian Kang Rudy Khoo, Demetrios Laoutatzis, J L Lindsay, Komanduri Kutumba Narayanacharyulu, R T H Shepherd, Ralph Shulman, V E R Spence, P F Wale, Alison S Wallace, G C J Wiernik, T S Worthy, Ying Yeung Yeung

D M R D—Theodore Chang, A R Chrispin, P F Claremont, A L Fletcher, Santi Pada Ganguly, Boris Golberg, E H Haynes, A E Hugh, Ivan Hyde, Aung Nyein, O F Paise, Ahmad Jerjees Shammaa, A J Slabber, D P Thomas, Vissarion Tzouliadis, E H Williams, J E Williams, S M Wolpert

D O—Nisar Ahmad, J H Armstrong, T C Barras, Inderjit Singh Bhar, Golok Chandra Bhattacharjee, J J Blake, G J Bougher, Dorai Chamarraj, Hari Charan, J A Cox, E W G Davies, H J A Hahn, John Harrington, A C Hayes, Man Lin Hooi, Don Manupala Samarasekara Karunaratne, David Learmont, Mohamed Noor Bin Marahakim, F O Mueller, Myint Aung, Thimmanniah Channakeshaviah Nagaraja, M C Peterside, Padmakar Shrikrishna Pradhan, Gopal Nandan Prasad, W E L Rees, Robert Renton, John Roberts, Kamal Mustafa Saleh, F C C Schwerdt, Elkan Silverstone, Bhrigunath Singh, Dwarka Prasad Tiwari, P G Watson, D J Wilson.

D T.M & H—Fawzi Tadros Abdel-Messih, R M Barnes, Gerald Bevan, R S Blewett, Hemraj Bodasing, D E Bradford, Narendra Kumar Chakravorty, Piti Changtrakul, Josephine Dobson, Nagendra Kumar Gami, Michael Gass, Ramachandra Eknath Godbole, Daniel Kelleher, Mohammad Aslam Khan, Houshang Khazrai, R F Knight, Stephen Leung Wing-Chiu, Adetokunbo Olumide Oluwole Lucas, Elizabeth M MacCrone, Mary I Malone, Khalid Rashid Minhas, Devendra Mohan, Abdol Baghi Nawab, H G Penman, Herbert Pullen, Abdul Majid Qureshi, Narasipur Srinivasa Iyengar Ramaswamy, Poul Erik Randrup, W M Robinson, Zafar Ali Sapru, Izzaldin Abbas Shikara, Khin Maung Tin, Margaret Tu, J R Wilson, William Young, Ahmad Junaid Yusuf, W L Zike

Royal College of Physicians of Edinburgh

On Wednesday, May 25, Mr F John Gillingham will give the Morison lecture He will speak on stereotactic surgery of the brain On Wednesday, June 8, Prof Robert Cruickshank will give the Lister fellowship lecture His subject will be measurements in medicine Both the lectures will be given at 5 P M at the college, 9, Queen Street, Edinburgh, 2

British Society for Immunology

A meeting of this society will be held at the London Hospital Medical College, Ashfield Street, E 1, on Friday and Saturday, May 20 and 21 The meeting will include a symposium on immunological aspects of diseases of connective tissue Further particulars may be had from Dr R G White, bacteriology department, London Hospital

Reciprocal Social Security with Germany

Reciprocal agreements on social security with Germany were signed on April 20 They cover all the benefits provided by the United Kingdom schemes of national insurance, industrial injuries insurance, and family allowances and the corresponding benefits in the Federal Republic of Germany and in Western Berlin The agreements will not come into force until they have been ratified

Institute of Hospital Administrators

The annual conference of this institute will be hel Scarborough from May 5 to 7 Sir Charles Morris will o the conference, and the programme will include a pape Dr R F L Logan on assessment of future hospital need

Cell, Chromosome, and Virus Microscopy

A lecture and demonstration on the use of microscop cancer research is to be given at the Royal College of Surg of England, Lincoln's Inn Field, London, W C 2, at 5 45 on Tuesday, May 10

The speakers will include Prof G J Cunningham, Prof P Koller, Dr R. J C Harris, Dr E J Ambrose, Mr M S C Birb Dr C M Clarke, Dr A J S Davies, Dr S H Revell, and E M F Roe A new system of colour television will be used and programme has been devised and coordinated by Prof Alex Haddow and Professor Cunningham The college is arranging medical students to see the lecture at 3 30 P M. on the same Tickets for both meetings may be had from Mr W F Davis a college

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The Yorkshire Society of Anæsthetists will hold a meetin Saturday, May 21, at 10 45 A M, at Huddersfield Royal Infir The speakers will include Dr C S Ward, Dr A R Kerr, Dr G Jackson Rees

The National Old People's Welfare Council have publish revised edition of their booklet on the organisation of a vis service by an old people's welfare committee In an append describes some schemes which have been started in country par and in towns, in Wales, the North, and the Midlands, and offers h ful points drawn from this varied practical experience Copies and 4*d* postage) may be had from the Council, 26, Bedford Sq London, W C 1

CORRIGENDUM *Placenta Prævia*—The first sentence of Mr Theobald's letter last week should have ended "sine HP", meaning without hypertension and proteinuria—i e, without toxæmia

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Appointments

COOK, A M, M.B Aberd, D P M psychiatrist (S H.M O), Stratheden Hospital, near Cupar, Fife

HARRIS, RUTH F, M.B Lond, D C H senior registrar, department of clinical neurophysiology, The Hospital for Sick Children, Great Ormond Street, London

HENDRY, R G, M B St And, D OBST, D P H senior M O, Hertford

JACKSON, J W, M CH Dubl, F.R C.S consultant thoracic surgeon, Royal National Orthopædic Hospital, London

MILLER, HAROLD, M D Lond, M R C P consultant pathologist, Portsmouth and Isle of Wight area pathological service

PAPATHEOPHILOU, RITSA, M.D Athens senior registrar, department of clinical neurophysiology, The Hospital for Sick Children, Great Ormond Street, London

PHILLIPS, D E, M R C S assistant M O, Liverpool

ROBERTS, H E, B M Oxon M O, Sheffield regional blood transfusion centre

THOMAS, H M, M B Lpool, D P H, D C H M O H and divisional M.O, Alderley Edge, Cheadle and Gatley, and Wilmslow, Cheshire

WILSON, D L, M.B Glasg, D T M & H assistant M O H and school M.O, Carlisle

WOOD, K F, M B Leeds, F R C.S part-time consultant general surgeon, Leicester General Hospital and associated hospitals

East Anglian Regional Hospital Board

ATHLEY, B A, M B Bombay surgical registrar (casualty), Peterborough Memorial Hospital

CHAUDHRY, J K, M.B Lucknow surgical registrar, Ipswich and East Suffolk Hospital

DAVIDSON, J R M, M B N Z, F R C S E. surgical registrar, Norfolk and Norwich Hospital

MACKINTOSH, A J, M.B Glasg registrar in obstetrics and gynæcology, West Norfolk and King s Lynn General Hospital

Oxford Regional Hospital Board:

HADFIELD, G J, M.S Lond, F.R C.S consultant in general surgery, Aylesbury/High Wycombe area department of general surgery

PRYER, R. R L, M.B Lond, F.R C.S consultant in general surgery, Aylesbury/High Wycombe area department of general surgery

SHRIBMAN, IRVING, M B Dubl, D P M consultant psychiatrist, St. John's Hospital, Stone

Colonial Appointments

ABAYOMI-COLE, A B, O B E., M.B Durh D D.M.S, Sierra Leone.

EVANS, A E J, M B Lpool M O, Bahamas

MCARDLE, J M, M B Edin M O, Uganda

MURPHY, J C. V, M B Lpool, D T.M & H, T D.D M O, Northern Rhodesia.

NARAIN, H B, M.B M O, Nigeria Northern Region

THOMAS, G M, M D Edin, M.R C.P E., D P H senior specialist, Hong Kong

WALLING, K E, M B St And, D P.H M O H, Mauritius

WHIMSTER, W F, M B Cantab M O, Fiji

YAP, PAO-MENG, M D Cantab, M.R C.P E, D.P.M senior specialist, Hong Kong

The Lancet · Saturday 7 May 1960

MEDICAL ASPECTS OF ROAD SAFETY *

L G NORMAN
M D, B Sc Lond, M R.C.P, D P H
CHIEF MEDICAL OFFICER, LONDON TRANSPORT EXECUTIVE

THE first two deaths registered in Great Britain as due to motorcars were in 1896, while the first fatal accidents caused by motor-cycles were in 1902 (Martin 1957) From these small beginnings a terrible stream of deaths has followed About 125,000 people have lost their lives in this country alone

In 1958, 5970 persons were killed—1264 of them under the age of 20 and 1013 between 20 and 30 In the same year, 69,166 were seriously injured This catastrophic loss and injury, particularly of the young, would undoubtedly have appealed to Gavin Milroy as a public-health problem demanding urgent attention The problem is unique All other epidemics throughout history have been due to the onslaught of external agencies, mainly the bacteria and viruses, but road accidents are caused by man himself The community's responsibility should be recognised and vested in one authority, particularly as much existing knowledge awaits application

Road, Vehicle, and Road User

The work of the Road Research Laboratory has resulted in many improvements in the design, construction, and lighting of roads

Vehicle

On vehicle design and construction McFarland (1956, 1957) recommended among other things the removal of dangerous projections, the fitting of recessed-hub steering-wheels to reduce chest injury, the use of sponge-rubber padding to cover dashboards, and the use of seat-belts But a higher standard of safety in the vehicle may mean a higher first cost, and manufacturers may not be able to reach this standard unless the public is willing to pay for it or forced to do so Provins (1958) reviewed the effects of low and high environmental temperatures, and of air pollution by carbon monoxide, on tasks related to driving Sustained temperatures below 50°F or above 87° appeared likely to impair driving efficiency, as did carboxyhæmoglobin levels above 12% Methods of measuring and improving visibility from the driving seat were reported on by Fosberry (1958) of the Motor Industry Research Association Studies of accident injuries in relation to the design and structure of the vehicles were undertaken at Cornell University (Moore 1957) This is the work on which recommendations for the use of seat-belts are based, for it showed that a frequent cause of fatal injury was ejection from the vehicle and that fatal and serious injuries were 80% fewer when seat-belts were used Gissane (1959) designed a safety-cap for use by motorists In Great Britain in 1958 the majority of the 1690 fatal accidents to vehicle drivers and passengers (Road Accidents 1958) were from head injuries, many of which would have been less serious if an efficient safety-cap had been worn

The Road User

Many studies have been made of the road user The Applied Psychology Research Unit, for example, has undertaken field studies of the actual task of driving Psychologists, however, deal with the normal human organism and make no allowance for drivers with ocular defects or systemic disease—conditions which we have to consider here At present, research in Great Britain covers only a small part of the work urgently required on human problems in road transport

Of the various road users, the vehicle driver is not alone responsible for accidents, but it is he who holds the potentially lethal instrument Driving is a *skill* which requires training, and, like other skills, it can be maintained at a high level only by regular practice In London Transport the average time taken to train a driver who has never driven before is fifty hours at the wheel, spread over at least four weeks, experienced drivers may require almost as long to "unlearn" their faults In some American States, drivers who have repeated accidents are sent to "driver clinics" for investigation and treatment Such a procedure would be valuable if it could be clearly established that a particular driver had in fact experienced an excessive number of accidents compared with other drivers of the same age and sex who drive the same number of miles annually under similar conditions These data are not generally available The most baffling characteristic of road-accident statistics is the extreme difficulty of constructing an "exposed to risk" formula against which to consider them

Epidemiology

The numbers of road casualties in 1926–58 are given in table I

TABLE I—CASUALTIES FROM ROAD ACCIDENTS, GREAT BRITAIN, 1926–58

Year		Average Annual Numbers		
		Killed	Injured	Total
1926–29	annual average	5762	154,554	160,316
1930–34		7041	206,879	213,920
1935–38		6586	225,663	232,249
1939–45		Recording incomplete		
1946–49		4807	159,948	164,755
1950		5012	196,313	201,325
1951		5250	211,243	216,493
1952		4706	203,306	208,012
1953		5090	221,680	226,770
1954		5010	233,271	238,281
1955		5526	262,396	267,922
1956		5367	262,593	267,960
1957		5550	268,308	273,858
1958		5970	293,797	299,767

The annual number of deaths reached a peak in the early 1930s, the highest recorded was 7343 in 1934 In the past twenty-five years there has been some improvement, but this should be regarded less as a reason for complacency than as evidence that reduction in the death-rate is possible (In 1952, for example, the deaths of pedestrians fell by over 10% this was the year in which zebra crossings were introduced) Since 1950 deaths have increased again, by about 20% The increase in numbers injured may have been partly due to more complete recording of minor injuries Some fluctuation was associated with motor-fuel rationing, which was in force, for example, from Dec 17, 1956, to May 14, 1957

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* Abridged from the first Milroy lecture for 1960, delivered before the Royal College of Physicians of London on Feb 2 The second lecture, with the references, will appear in a forthcoming issue

The numbers of deaths from road accidents and from certain other conditions in 1957 are shown in table II

In 1957, for the first time, deaths in road accidents exceeded those from all forms of tuberculosis Deaths from diphtheria, whooping-cough, and acute poliomyelitis together were only a fifteenth of those caused by traffic accidents The crude death-rate from road accidents at all ages is about equal to that from diphtheria in London in 1880–90 (Newsholme 1935) In males road accidents caused more deaths than tuberculosis, diabetes mellitus, chronic rheumatic heart-disease, peptic ulcer, or nephritis Accidents in the home are about equally numerous, causing some 8000 deaths a year

Road accidents are now the commonest cause of death in male adolescents and young adults As fig 1 shows, about a third of all male deaths in the years of promise, 20–24, are caused by road accidents Morris (1955) estimated the chances that a man of 35 will sustain severe injury in a traffic accident before reaching the age of 65 as about 3%—and these are the safest years

The road deaths in Great Britain in 1957 according to age and class of road user are shown in fig 2 These figures are gross totals and take no account of the exposure-to-risk The groups on which education, including propaganda, is focused are the young (male) motorcyclist, the child cyclist, and the elderly pedestrian

TABLE II—DEATHS FROM CONDITIONS SPECIFIED, GREAT BRITAIN, 1957

International List no	Condition	Deaths		
		Males	Females	Total
E810–E835 E840–E845	Road vehicle accidents	4186	1364	5550
001–019	Tuberculosis (all forms)	3898	1609	5507
055	Diphtheria	2	4	6
056	Whooping-cough	43	66	109
080	Acute poliomyelitis	150	87	237
260	Diabetes mellitus	1158	2484	3642
410–416	Chronic rheumatic heart-disease	3292	5812	9104
540, 541	Peptic ulcer	3993	1600	5593
550–553	Appendicitis	564	338	902
590–594	Nephritis and nephrosis	2597	2273	4870
660, 670–678	Maternal mortality		109	109

The mortality in road accidents per million living, by age and sex (fig 3) emphasises the high rate in young adult males and in people over 70 There were 1057 road fatalities over the age of 70 in 1958, 904 (85%) of which affected pedestrians The high death-rate in elderly male pedestrians is striking Octogenarians were at least 20 years old in 1900, they grew up in the horse-and-buggy days and perhaps do not appreciate the high speed which oncoming modern vehicles may attain, nor the effect of their own reduced agility Drivers, particularly young drivers, should be taught these mortality *findings so as to give them a sense of care for elderly and* perhaps infirm pedestrians 40% of all fatal road accidents are to pedestrians

A new era in prevention began with the studies of the late Sir Hugh Cairns on head injuries He showed that most deaths of motor-cyclists were from head injury and advocated safety-helmets, but, even now, only about half the young men and women motor-cyclists wear them In 1953–54 head injuries still accounted for 80% of fatal accidents to motor-cyclists (Grime 1958)

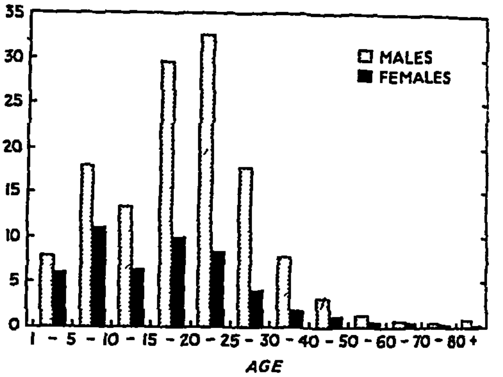

Fig 1—Percentages of total deaths due to road accidents Great Britain, 1957

Table III shows that motor-cyclists are second to pedestrians in numbers killed The large number of pedestrians killed shows the advantage to be gained if access were controlled, as on the railways The relatively high rate of fatal accidents to motor-cyclists is shown in table IV Clearly, parents and young men—and their pillion companions—should be warned of the dangers of motor-cycling without adequate head protection

But the statistical picture is not all black Since 1930, the number of fatal accidents has fallen steadily in relation to the number of vehicles licensed (fig 4) The *number per thousand vehicles registered decreases* with increase in the number of vehicles using the roads As the number of vehicles increases, people apparently become more skilled in avoiding accidents (Glanville 1954) Perhaps the increasing intensity of traffic prevents people from behaving as dangerously as they might But it seems unlikely that we are yet motorising ourselves into a state of safety, and other reasons are probably responsible for this reduction in accident-rates

In the United States road deaths fell from 39,628 in 1956 to 38,702 in 1957 and 37,000 in 1958—a reduction of 7% in three years Over the same period fatal road accidents in Great Britain increased from 5367 to 5970 In the United States the death-rate per 10,000 vehicles registered in 1958 was 5 7, the lowest recorded (National Safety Council 1959), the corresponding figure in Britain was 8 0 (Road Accidents 1958) The lower figure in the United States may be associated with the lower proportion of vehicles to miles of road Britain has the highest proportion of vehicles to miles of road of any country

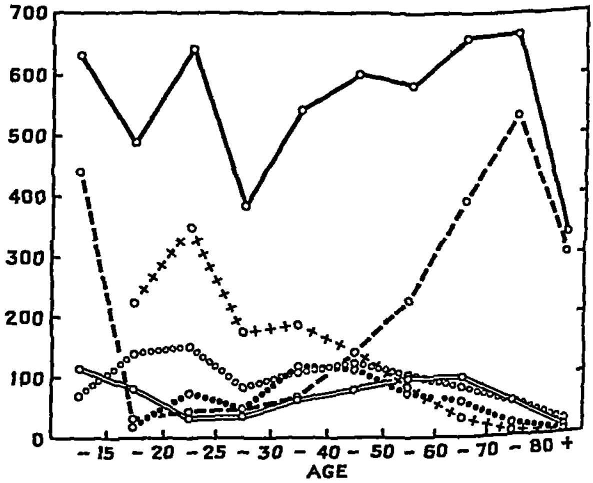

Fig 2—Number of deaths in road accidents according to age and class of road user Great Britain, 1957

TABLE III—DEATHS IN ROAD ACCIDENTS, GREAT BRITAIN, 1957

Class of road user	No of deaths
Pedestrians	2225
Motor-cyclists	1157
Moped-riders	47
Drivers of other vehicles	529
Pedal-cyclists	663
All passengers	929
Total	5550

In 1958 the death-rate in road accidents per 100 million vehicle-miles in the United States was 5 6, the lowest recorded, the corresponding figure in Britain was 10, also the lowest recorded

The basing of fatalities on a denominator of total population figures is of limited value in the study of road-accident mortality trends While the population has remained roughly constant, the number of motor vehicles registered has approximately doubled in the past ten years It is therefore more realistic to use the number of miles actually travelled by road vehicles each year as the denominator for the calculation of mortality-rates This mileage is obviously difficult to determine, but reasonably accurate estimates are given in Road Research (1958) The numbers of vehicle-miles travelled per annum are given for different types of road vehicle, but no estimates can be made of the annual mileages travelled according to age and sex

TABLE IV—DEATHS PER MILLION VEHICLE-MILES, GREAT BRITAIN, 1956

—	No of deaths	Millions of vehicle-miles travelled *	Deaths per million vehicle-miles
Motor-cyclists (including 176 passengers)	1250	4500	0 27
Occupants of other vehicles	1197	47,200	0-025

* Chandler and Tanner (1958)

Fig 5 gives the mortality in recent years according to vehicle-mileage travelled Until 1954 there was a steady decline in the death-rate, expressed as mortality per million vehicle-miles, but since then there has been no improvement This is probably one of the most useful statistics to indicate trends in mortality, but it takes no account of such factors as the ageing of the population Studies of the death and accident rates in the several different ways described above are therefore required for a more complete picture of mortality trends

Sex of Drivers and Accident-rates

Contrary to popular opinion, there is little evidence to show whether male or female drivers are the more liable to accidents

Lauer (1952) analysed the reported accidents of men and women in Iowa After allowing for women holding only a quarter of the licences, and after estimating that they drove only about a tenth of the total mileage, Lauer found no real difference between the accident-rates of men and women drivers A curious finding was that men improved their accident records after about five years' experience whereas women showed an improvement after the first year This observation has not been confirmed by other workers

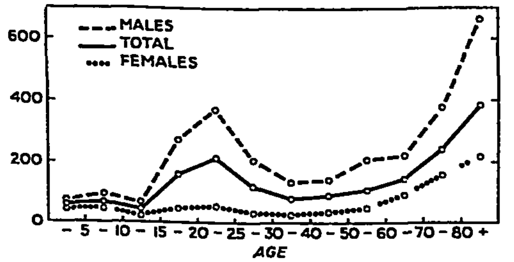

Fig 3—Mortality in road accidents, by age and sex, per million living Great Britain, 1957

Viteles and Gardner (1929) studied the accident experience of groups of men and women taxi-drivers and found that the women had fewer serious accidents than the men The value of this study is limited, however, because the groups of men and women were not evenly matched for previous driving experience

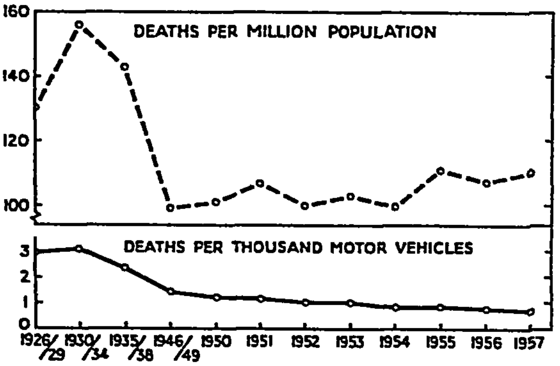

Fig 4—Number of deaths in road accidents per million population and per thousand motor vehicles Great Britain, 1926-57

A study of Connecticut drivers (U S 75th Congress 1938) suggested that accidents per driver were fewer among women than men, but differences in exposure to accidents could not be fully taken into consideration

Until strictly comparable groups of men and women drivers can be obtained, the existence of a sex difference in accident liability remains unknown Studies of this factor might be of value, not merely to settle a difference of opinion between the sexes, but also as a lead to the further study of the reasons for any dissimilarity observed

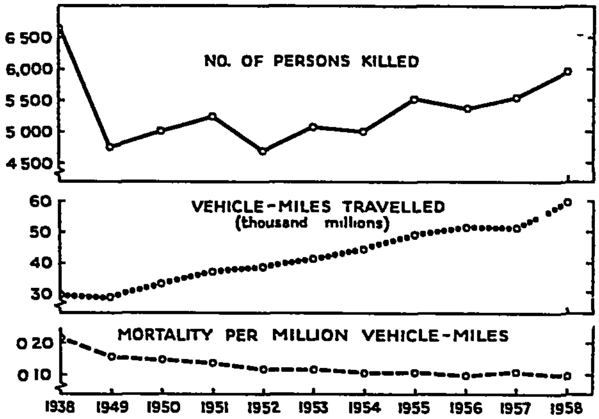

Fig 5—Mortality in all types of road accidents per million vehicle-miles travelled Great Britain, 1938 and 1949-58

Age of Drivers and Accident-rates

Below the age of about 65, younger drivers have more accidents than older ones Thus McFarland et al (1954), studying accident-rates of professional truck-drivers, found that the older men were less liable to accident Again, Lauer (1952) found that among drivers of private cars those under 30 had the highest accident-rate.

The results of a study of the accident experience of London Transport drivers, by age, are given in table V

TABLE V—LONDON TRANSPORT CENTRAL BUS DRIVERS
AVERAGE NUMBER OF ACCIDENTS PER DRIVER PER ANNUM

Age attained in year of observation	Length of service as driver (years)				
	Under 4	4–8	9–13	14 and over	All service groups
Under 30	2 409	1 770			2 386
30–39	1 861	1 129	0 815		1 494
40–49	1 576	0 943	0 832	0 677	1 077
50–59	1 402	0·998	0 833	0 645	0 836
60–64	1 316	0 869	0 934	0 623	0 728
Under 65	1 876	1 022	0 843	0 640	1 173
65	*	*	*	0 775	0 807
66				0 642	0 725
67				0 727	0 749
68				0 673	0 712
69				0 723	0 753
70				0 825	0 889
65 and over				0 721	0 766
All ages	1 876	1 002	0 843	0 650	1 159

* There are too few drivers over the age of 65 with less than 14 years service to enable reliable rates to be calculated

The average numbers of Central Bus drivers employed in 1957 and 1958 were 13,856 and 13,052 respectively, giving a total man-years of exposure for the two years of 26,908 All accidents, including minor ones involving no personal injury, were recorded, and totalled 31,198 Age is, of course, closely correlated with experience, and in order to study separately the effects of age alone, the drivers were divided into groups with different lengths of service These men are all professional drivers who drive for about seven hours each working day of their lives On average, a driver travels about 18,000 miles a year, and after fourteen years he will have driven about 250,000 miles, all in London traffic

Table v shows that drivers under 30 have relatively high accident-rates, and for drivers with less than four years' service there is a steady improvement with increasing age In the middle ages, the accident-rates of drivers with more than four years' experience show little variation with age Experience has more effect than age London Transport drivers may continue to the age of 70, subject to annual medical examination from 65 onwards The number of drivers remaining in the service after 65 is relatively small In fact, about half those who remain in the service until the age of 65 then retire voluntarily, so that those who continue after this age are a highly selected group Nevertheless, the average accident-rate for these older drivers was 13% higher than the average rate for men under 65 with similar driving experience Both rates are, however, notably lower than the rates for younger drivers with less than fourteen years' experience The accident-rates for these older drivers appear to vary somewhat erratically with age, but these variations show some similarities with the retirement-rates of drivers and conductors Retirement over 65 appears to take place as a process of continued selection—the fittest survive—so that an increase in retirements leads to a decrease in accidents

Drivers of *all* ages with very short service have much higher accident-rates than drivers with long service If this effect applies also to drivers of private cars, a practical application would be to continue training by means of occasional demonstrations and lectures during, say, the first two years after a licence is obtained The inexperienced driver who drives only occasionally brings a double hazard on to the roads

Much interest centres on the accident-rates of elderly drivers, but there are no reliable statistics of accident-rates of drivers over the age of 70 Insurance companies, before issuing a policy, sometimes require drivers over this age to submit a medical certificate of fitness to drive They may have had unfavourable experience with these elderly drivers, and with some other classes of drivers, but their records do not provide satisfactory material for a study of accidents in relation to age There are several reasons for this (Johnson and Garwood 1957) for instance, the insured car may be driven by different drivers at different times and accident experience is not therefore confined to the elderly owner-driver alone Administrative action has, however, been taken in some countries In New Zealand, from the age of 70 *all* drivers have to submit an annual certificate of medical fitness The examinations thus necessitated sometimes place the family doctor or the consultant friend in difficulties, and it is suggested that they should be made by independent practitioners In Portugal, medical examination is required before the issue of all licences, and these examinations are undertaken by a few specially appointed practitioners, this has also the advantage of maintaining a uniform standard There is provision for an appeal against rejection

Applied Psychology

The number of miles which the average driver travels before having an accident is impressive When one considers the achievements of human beings on the roads in a detached way (for instance, by trying to think what sort of automatic device one could introduce to do the job instead) one is lost in admiration for their success In 1958, the average driver would have had to travel about 200,000 miles before being involved in an accident resulting in injury to a person At an average speed of 25 miles an hour, this represents a driving time of about eight thousand hours As the average development time for an accident is probably about five seconds, or even less, drivers appear to possess remarkable powers of concentration Perhaps the limit of human performance in this respect is being reached, but this unhappy view should not be accepted too readily

The problem here is essentially one of vigilance Mackworth (1950) found that vigilance was affected by environmental conditions and that people differed greatly in their abilities on the tests, but no reason could be discovered for these differences, which were unrelated to visual acuity or intelligence-test score One practical application of vigilance studies lies in the teaching of anticipation, a very important quality for driving

In spite of the emphasis placed on tests of reaction-time, the skill of driving—so far as it is related to accident prevention—does not depend solely on quickness of reaction It seems obvious at first sight that drivers with the shortest reaction-times should be able to act most promptly in the accident situation and thus have fewer accidents than more slowly reacting drivers That this idea may be misleading is shown by the fact that drivers aged 18–25, who have the shortest reaction-times, experience more accidents than middle-aged drivers Young drivers give a better performance on psychokinetic tests generally Allgaier (1938), for example, found that the tapping test was best performed in the 20s and that the best scores in a simulated driving task *in a motor-trainer* were given by drivers aged 15–25 It appears that as a man ages in the middle range, his reactions are slower, his hearing diminishes, his eye-hand coordination deteriorates—*but he becomes a safer driver* This is probably because an essential part of the driving skill is the avoidance of accident situations, a factor which appears to be better developed in the middle-aged than in the young Avoidance of the accident situation depends on the degree of care exercised, on experience, on the important quality of anticipation, and perhaps on other factors as yet unrecognised

Laboratory and field studies of the nature of the driving task should provide information about the qualities required for safe driving. It is assumed—but the assumption may not be correct—that these qualities can be taught in their just proportions, and that the work of the psychological laboratory can be applied in the driving school. Laboratory studies are likely to be of use in improving the method of training more than its content, and perhaps in eliminating people who are defective in crucial qualities—if these can be identified (Broadbent 1960). The two main lines of investigation are (1) studies of the fundamental nature of human performance in relation to driving, and (2) the application of the results of applied psychological research to the training of drivers and other road users. There is need for an analytical study of the qualities required in driving, most of which can at present be approximately named and described but cannot yet be quantified.

Many studies have been made of accident-proneness. But the working environment of each driver is different, his exposure to risk of accident depends on such factors as the type of vehicle, the distance driven, and whether driving is mainly by day or night, in town or country. Even under the apparently constant conditions of London bus-routes, accident-rates are three times as high on some routes as on others.

There is, however, little satisfactory evidence to show that an individual driver's liability to accidents remains constant, nor has it been shown that a group of highly accident-prone drivers can be clearly separated from the rest. As Moore (1956) states, the most that can be said is that if all drivers had similar tasks there would be a group of accident-prone drivers, the size of which could be fixed by some arbitrary dividing line separating the prone from the not-prone. To prohibit people from driving on the ground that they belong to such a group would almost certainly be unjust in some instances. A study of 1000 public-service drivers in Finland was undertaken by Häkkinen (1958), who obtained a correlation of over 0·6 between the number of accidents experienced in one four-year period and the number of accidents experienced by the same drivers in the ensuing four years. This certainly shows that some drivers are likely to have accidents consistently, but Hakkinen was unable to find a reliable method of identifying accident-repeaters by laboratory experiment. It is important to distinguish between knowing that such people exist and being able to identify them.

In any one year in Great Britain, about 4% of the drivers have all the personal-injury accidents, but these drivers are not necessarily accident-prone. To study their proneness we should need to know whether they were involved in accidents in the following year, and this information is not available. Hence there is a tendency to replace the term "accident-prone" by "accident-repeater."

A recent study in this country is that of Davis and Coiley (1959), who defined accident-prone drivers as those who had sustained three or more accidents reported to the police between 1946 and 1958. Though their results did not confirm McFarland and Moseley's (1954) observation that accident-repeaters show personal qualities not found in safe drivers, Davis and Coiley draw attention to deficiencies in their own method of sampling and discuss plans for further research. It is surprising that this is the only investigation undertaken in the past twenty years in this country on drivers who have repeated accidents. Further research is urgently needed to determine whether there is a group of constantly accident-prone persons among road users. If such a group could be identified, remedial measures might well include additional training. The community would have to decide whether to withdraw licences from substantially accident-prone drivers, temporarily or permanently.

Skilled activities, such as driving, tend to become disorganised under emotional stress. Emotional states also influence what is perceived in a situation, and inadequate or inappropriate reactions may be made by emotionally disturbed drivers, leading to a condition of temporary accident-proneness. Instances of accidents which occurred when drivers had been emotionally disturbed are well known, but nothing is known of the importance of such factors in the total of road accidents.

Psychological tests of many kinds have been applied to drivers in an attempt to distinguish those more liable to accidents from those less liable. Some of these tests, such as those of eye-hand coordination, of simple motor speed, and of choice-reaction, are performed worse by groups of drivers who have repeatedly had accidents than by the relatively accident-free. There is, however, considerable individual variation and it is not yet possible to use the results of such tests with any degree of accuracy to predict the performance of any one individual as a driver. The search for stable psychological characteristics of drivers which are significant in causing accidents has in general proved disappointing, but the study of psychosocial and temperamental factors appears more promising than the traditional approach by way of sensory and psychomotor abilities. Thus McFarland and Moseley (1954) developed a method of objective study which has identified certain personality characteristics among a group of drivers who had repeated accidents. These characteristics include egocentricity, aggressiveness, antisocial trends, and social irresponsibility, and their study led McFarland to formulate his view that "a man drives as he lives." This "style-of-life" approach provides a useful working basis for the selection of professional drivers, but its validity depends on the assessment of personality, which is notoriously difficult to measure. A curious anomaly is that some people who are quite reasonable in ordinary life become unreasonable when driving a motor vehicle.

It is possible that fatigue is a common cause of accidents. In Great Britain in 1958, among the 165,832 incidents reported to the police in which a personal contributory factor could be identified, there were only 409 in which fatigue (or "asleep") in a driver or cyclist was given as a contributory factor, but the police reports are likely to be incomplete in respect of fatigue. On the Pennsylvania Turnpike in 1952 and 1953, a driver was asleep in 13·2% of all accidents (Glanville and Moore 1955). In an unchanging environment vigilance decreases, and a lack of variation in perceptual stimulation may induce drowsiness. One practical application of this lies in the design of trunk roads, which should perhaps include factors to preserve the driver's alertness. There is no generally accepted definition of fatigue, but useful advice may be given to drivers about the need for adequate rest periods before driving, and about the advisability of resting for a few minutes every two hours or so on a long drive.

The concept of skill-fatigue, developed by Bartlett (1943), may be of importance in road accidents. A distinction is necessary between the type of fatigue produced by continued physical effort and that produced by a task requiring little muscular exertion but persistent concentration and a high degree of skill The latter type of fatigue tends to occur during the first hours of work A typical example is that of the driver at night who " halts at an intersection where there is no traffic light and waits patiently for the green, then, 'pulling himself together', he dashes on, intent on the clear roadway ahead, and deriving no meaning from the headlights he sees approaching from the side " (*Lancet* 1957) Further studies will no doubt be undertaken on the nature of skill-fatigue At present the only practical application might be to inform learner-drivers of the existence of this condition It may be that some accidents at present attributed to such vague and rather meaningless factors as absentmindedness, lack of concentration, and inattention are in reality due to skill-fatigue

Davis (1958) thought that explanations of accidents in terms such as lack of concentration and absentmindedness are unsatisfactory because either they do no more than give a name to what has obviously happened, or they suggest a cause without giving any insight into the way in which it might have operated to produce the particular accident

Drugs and Driving

A reasonably efficient degree of human performance in many respects is necessary for the safe driving of a motor vehicle, and human performance may be adversely affected by many drugs which are in common use today, some of them obtainable without prescription How far the use of drugs contributes to road accidents is unknown Accidents in which a road user was noticeably under the influence of a drug are certainly rare, but the desirable clinical effect of mild sedation or the attempt to induce peace-of-mind by chemical means may affect driving safety No laboratory studies on drugs, comparable with those on alcohol and driving, have so far been undertaken Medical practitioners who prescribe drugs which may affect driving safety presumably have a duty to inform patients of the possible dangers of driving after taking the drug Many patients are drivers, and there is here an added responsibility which must lie with the prescriber, unless he is told, the patient cannot be expected to know the possible effects and side-effects of the drug he is taking For example, a bus driver was recently prescribed chloroquine sulphate, 800 mg daily, at hospital The side-effects of chloroquine include deposits in the cornea, paralysis of accommodation, and occasionally vertigo This driver was advised at hospital to resume his normal work, no reference being made to his occupation

Truly, as Donald Hunter has said, we are passing from the age of dangerous surgery and entering the age of dangerous medicine (Rose 1958) When I was a student it was sometimes cynically said that the only diseases we could cure were impetigo and scabies and not always those Now there are powerful drugs to lower the blood-pressure, to alter the personality, to change the blood-chemistry, and some of these drugs may induce conditions which can adversely affect the patient as a vehicle driver Hypnotics, sedatives, and tranquillisers should be prescribed with caution for drivers The side-effects of anti-histamines vary considerably, and patients on these drugs should not drive until they have established by trial that they do not experience significant side-effects Patients on ganglion-blocking agents should generally be advised not to drive, but other hypotensive drugs are probably safe where postural hypotension is not produced The group of central-nervous-system stimulants, of which amphetamine is probably the most often prescribed, temporarily increase alertness and efficiency, but large doses may induce headache, agitation, irritability, and impaired concentration—in short, a condition of unfitness to drive Fatigue and depression normally follow the initial stimulation Miller (1957), who suggests that long-distance lorry drivers may be particularly exposed to this hazard, recommends that if the dosage of amphetamine does not exceed 10 mg, a driver may be permitted to prolong driving for a period not exceeding two hours, the drug should not be repeated on the same day But in the interests of safety, drivers should probably be discouraged from taking any such drugs at all

Patients under treatment with certain drugs, such as barbiturates, should be warned of the additive effects of alcohol Many people, and probably many drivers, are now taking barbiturates or tranquillisers, and they should be made fully aware that the combined effects of alcohol and the drug may seriously impair their driving safety, even with an amount of alcohol which they would normally regard as " safe "

Alcohol and Driving

In 1938 a committee of the House of Lords (H L 52 Committee) said that " propaganda should be employed to train and fortify public opinion in the condemnation of persons who drink before driving—above all, to discourage the practice of 'one for the road' " A report on present knowledge of the relation of alcohol to road accidents has been published by the British Medical Association (1960)

Drew et al (1959) studied the effect of measured blood-alcohol levels on the performance of 40 subjects in an experimental task resembling that of driving a vehicle on the road With the low blood-alcohol levels reached there were no clinical signs of intoxication apparent to trained observers Nevertheless, three-quarters of the subjects tested showed a measurable impairment of performance, this is the important finding The chief problem is not the driver who is so intoxicated that he is physically unable to drive The danger is with subclinical intoxication, in which a driver appears normal under clinical examination but his driving safety and efficiency are impaired

The conclusion is inescapable that the consumption of alcohol by road users is responsible for a considerable proportion of road accidents This is one of the most important problems in the promotion of road safety today

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" Most people came into the service The position of health in this respect has differed strikingly from that of education The middle classes have found it more acceptable to go to a Health Service doctor or dentist than to send their children to state schools This has been as much an advantage to the development of the service as it has been a disadvantage to the development of public education It will be a great misfortune if access to private practice is made so easy as to restore the position where there is one standard of treatment for the better off and another for the rest " —*New Statesman*, April 30, 1960, p 632

ANTICOAGULANT THERAPY IN ACUTE CEREBROVASCULAR ACCIDENTS

A CONTROLLED TRIAL

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AT present no specific form of medical treatment is of proven benefit for patients with a "stroke". Vasodilator drugs, corticosteroid therapy, and stellate-ganglion block have all been tried, but none has been proved of value when subjected to controlled clinical trial. This does not mean that medical treatment has no influence upon the acute illness. The appropriate application of supportive measures substantially affects mortality and the degree of functional recovery in survivors; these measures include physiotherapy for paralysed limbs, and the maintenance of fluid and electrolyte balance, nutrition, and pulmonary ventilation. But as yet neither the intracranial lesion nor its immediate effects upon nervous structures can be favourably modified.

Although the precise pathogenesis of many acute cerebrovascular lesions is uncertain, thrombosis is undoubtedly one of the mechanisms involved, and by analogy with their apparent usefulness in occlusive vascular disease in other sites, it seemed reasonable to postulate that anticoagulant drugs might be of benefit in cerebrovascular disease.

Hedenius (1941) first described their use in this context, but, although his impressions were favourable, his results were inconclusive. As with coronary-artery disease, therapeutic evaluation of these drugs in cerebrovascular disease has been slow and difficult, and some of the reasons have already been discussed in relation to long-term treatment (Hill, Marshall, and Shaw 1960).

In the acute stroke the principal difficulty lies in making a correct pathological diagnosis, for the same clinical picture may result from interruption of the same neural pathways by many different processes. Some are hæmorrhagic, as opposed to ischæmic, and obviously unsuitable for anticoagulant treatment. This distinction can sometimes be made reasonably accurately on the basis of such features as bloodstained cerebrospinal fluid, but no invariably reliable distinguishing criteria are known. For this reason the clinically descriptive terms stroke and cerebrovascular accident are considered preferable to labels such as cerebral thrombosis, which imply an accuracy in pathological diagnosis which present knowledge seldom justifies.

The other main difficulty in using anticoagulants for acute cerebrovascular accidents has been the fear that anæmic cerebral infarcts may become hæmorrhagic. This is based on theoretical grounds (Symonds 1956, Brain 1957) and on animal experiments (Wood et al. 1958), but in trials of anticoagulant therapy in cerebral infarction, both embolic and non-embolic, Carter (1957, 1959) did not encounter this complication.

In Carter's embolic series (1957) the progress of twenty-six patients who had anticoagulants for 14 days after the acute incident was contrasted with that of thirty-four patients not so treated; the mortality was lower and the number of recoveries greater in the treated group. Wells (1959) observed a similarly encouraging result in acute embolic infarction.

In his study of fifty-six cases of non-embolic cerebral infarction treated with anticoagulants, Carter (1959) found that those whose stroke was of slow onset might be helped, but not those with hemiplegia of sudden onset. Rose (1950) found no benefit from anticoagulants in non-embolic cerebral infarction; twenty-four treated patients progressed no better than might have been expected without treatment, and two died of cerebral hæmorrhage during treatment.

Ushiro and Schaller (1957) gave anticoagulants to twenty-six patients with cerebrovascular accidents, but they did not distinguish between thrombotic and embolic cases; comparing the results with those in thirty-nine similar but untreated cases, they found no appreciable difference in the mortality-rate, the incidence of complications, or the natural course of recovery. Fisher (1958), however, reported more favourably on anticoagulants used in fifty-eight patients with cerebral thrombosis at various stages. He divided them into five groups, ranging from those who experienced transient ischæmic attacks only with no significant neurological deficit, to those with a fully developed stroke and maximum neurological deficit. Only the last group was not improved, and Fisher emphasised the value of anticoagulants in the progressively evolving stroke.

Millikan et al. (1958), from wide experience of anticoagulant therapy in various types of cerebrovascular disease, concluded that the four main indications for its use are: (1) intermittent insufficiency in the vertebrobasilar system, (2) intermittent insufficiency in the carotid system, (3) thrombosis in the vertebrobasilar system with infarction, and (4) actively advancing occlusion of the carotid system.

While these studies may suggest that anticoagulants are of value in particular situations they do not provide an adequate basis on which to decide for or against anticoagulant therapy in the majority of individual patients with a stroke. We therefore planned the present trial in an attempt to assess the value of anticoagulants in relation to the common therapeutic problem of the acute cerebrovascular accident of recent onset, when a hæmorrhagic causal lesion has been excluded as far as possible clinically, but regardless of the precise anatomical site of the occlusion. We decided to exclude cases of cerebral embolism resulting from conditions such as rheumatic heart-disease or myocardial infarction, because they differ in many respects from the more common non-embolic infarctions, and because others had suggested that their response to anticoagulant therapy is different. In cases of embolism there is often no intrinsic disease of the cerebral arteries, whereas such disease may influence the anastomotic circulation in non-embolic cases.

All patients in the trial were submitted to cerebral angiography, although we realised that this might be neither necessary nor practicable should anticoagulants prove generally beneficial in acute strokes. Our aim was to improve diagnostic accuracy and to assess the value of angiography in this respect (Bull, Marshall, and Shaw 1960).

In view of the difficulty of assessing therapeutic results in a condition of such variable and unpredictable pattern, we considered it essential to test anticoagulants in a strictly controlled trial. Its primary aim was to assess the influence of anticoagulant therapy on the immediate mortality—i.e., within 6 weeks of the cerebrovascular accident—but, in addition, any possible effects on late mortality or recurrence were sought by regular follow-up of patients after discharge from hospital.

The Trial

Method

Patients included in the trial were under 70 years of age During the 72 hours before admission to hospital they had sustained severe and persistent disturbance of brain function thought to be due to an acute cerebrovascular lesion other than hæmorrhage, extradural or subdural hæmatoma, aneurysm, or arteriovenous malformation, and provided no source of embolism was apparent in the heart.

Because the majority of patients were sent by the Emergency Bed Service and were not referred as diagnostic neurological problems no unusual selection operated at this stage The diagnosis was based on the history, clinical examination, lumbar puncture to confirm the absence of blood from the cerebrospinal fluid, plain radiographs of the skull, and angiography of the appropriate cerebral vessel While appreciating that more extensive angiography might sometimes be more informative, we decided to limit the examination to a single vessel (carotid or vertebral) to maintain uniformity Patients with severe hypertensive retinopathy, left ventricular failure, evidence of peptic ulceration, bleeding disease, or severe hepatic or renal disease, were excluded from the trial

TABLE I—AGE AND SEX DISTRIBUTION OF PATIENTS

Age (years)	Treatment group			Control group		
	Males	Females	Total	Males	Females	Total
30–39	1	1	2	0	2	2
40–49	4	3	7	0	3	3
50–59	7	6	13	4	5	9
60–69	2	2	4	6	5	11
Total	14	12	26	10	15	25

Patients regarded as having a non-embolic infarction after the above investigations were included in the trial only if the investigations had been completed so that *treatment could be started within 72 hours of the onset* of the illness They were randomised in pairs between two groups, no attempt was made to match them on the basis of age, sex, or any particular feature of their disease One group had anticoagulant therapy, and the other acted as control

The patients in the treatment group received an initial dose of phenindione (' Dindevan ') 300 mg by mouth or by intragastric tube 12 hours after angiography they were given three doses of heparin (12,500 units) intravenously at 6-hourly intervals Earlier administration of heparin has occasionally caused excessive bleeding from the site of arterial puncture From the 2nd day onwards, treatment was continued with phenindione twice daily by mouth, the dose being regulated by daily prothrombin estimations using the Quick one-stage test. The prothrombin-time was kept at two to three times the control time, treatment was continued for 21 days and then gradually withdrawn Both treatment and control groups were given the same general care and physiotherapy Uniformity in the management of both groups is important because factors such as bronchial obstruction and pulmonary infection, urinary infection, and fluid or electrolyte imbalance influence mortality

Because of uncertainty regarding the efficacy and hazards of anticoagulant treatment, it was desirable to subject the results to continuous analysis so that the trial might be concluded immediately a definitive answer emerged Classical tests of significance are generally inappropriate for this type of analysis, and the sequential method (Armitage 1954) was therefore adopted

The Patients

Fifty-one patients were included in the trial, twenty-four men and twenty-seven women Twenty-six patients were treated, and twenty-five served as controls The distribution by age and sex to the two groups is shown in table I Fourteen patients (27%) in the series were below the age of 50 Table II shows the anatomical site of the vascular lesions as judged clinically or angiographically In thirteen instances, including all the cases of internal-carotid thrombosis, the occluded vessel was demonstrated angiographically

TABLE II—SITE OF LESIONS

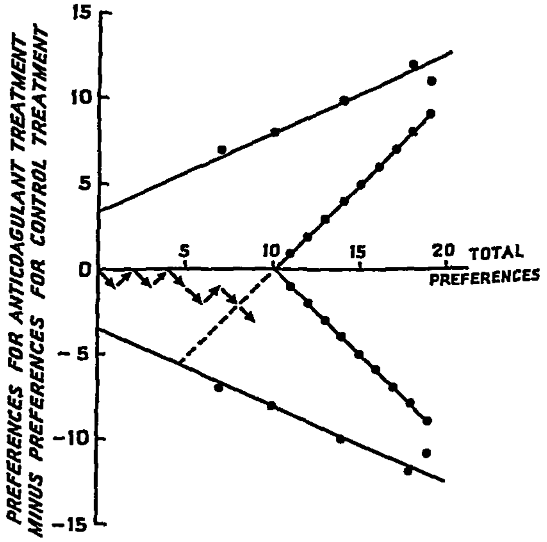
Site	Treatment group			Control group		
	Males	Females	Total	Males	Females	Total
Middle cerebral	10	9	19	4	10	14
Anterior cerebral	0	0	0	2	1	3
Internal carotid	2	2	4	2	2	4
Vertebrobasilar	2	1	3	2	2	4
Total	14	12	26	10	15	25

The incidence of hypertension on the basis of initial hospital blood-pressure readings is misleading because the intracerebral lesion itself may cause elevation or depression of the blood-pressure, an accurate premorbid reading is seldom available. But taking the mean of all hospital readings, including those in the recovery phase, ten patients had a mean diastolic pressure of 110 mm Hg or above, of these four were in the treatment group and six were controls

Results

The figure shows the sequential chart on which were plotted the results as they became available Survival or failure to survive for 6 weeks from the start of treatment was the criterion on which results were based

On admission to the trial patients were randomised in pairs, one to the treatment group and the other to the control group The analysis took cognisance only of those pairs in which the two members behaved dissimilarly—i e , one survived while the other died (untied pairs), no regard was taken of pairs in which both members survived or both died (tied pairs) When in an untied pair the treated member died, an arrow was plotted pointing downwards and to the right, whereas when a control member died the arrow pointed upwards and to the



Restricted procedure for $\theta = 0\ 9$ with maximum number of preferences, $n = 19$

Suppose θ is probability of preference for anticoagulants

If $\theta = 0\ 5$ (null hypothesis), probability of reaching each outer boundary is 0 022 (i e., slightly lower than the nominal 0 025)

If $\theta = 0\ 9$, probability of reaching upper boundary is 0 97 (i e , slightly higher than the nominal 0 95)

(Points at which the boundaries can be reached are shown as circles.)

TABLE III—RESULTS OF TRIAL

Result	Treatment group	Control group
Early (within 6 weeks)		
Deaths	6	3
Further ischæmic episodes	0	2
Late (6 weeks to 6 months)		
Deaths	2	4
Further ischæmic episodes	3	0

right. The horizontal axis thus represents the total number of untied pairs. The vertical axis represents the number of untied pairs showing preference for anticoagulant treatment minus those showing preference for control treatment. Thus if the apex of the plot registers a plus value it indicates a trend in favour of anticoagulant treatment, whereas a minus value (as in the figure), favours the control.

The statistical design was a "restricted procedure" of the type tabulated by Armitage (1957), but further calculations made since 1957 allowed the maximum number of untied pairs to be reduced from twenty-two to nineteen, and the appropriate boundaries are shown in the figure. If the plot had reached the upper boundary, it would have indicated a difference in favour of anticoagulants, or if it had reached the lower boundary, it would have indicated a difference in favour of the control treatment. Achieving either of the end boundaries would mean that no significant difference exists between anticoagulant and control treatment.

TABLE IV—CAUSES OF DEATH

Treatment group				Control group			
Case no.	Sex	Age (yr.)	Diagnosis	Case no.	Sex	Age (yr.)	Diagnosis
74977*	M	57	Brain-stem infarction	74923	F	69	Brain-stem infarction
76755	F	37	Cerebral infarction	78659	M	58	Bilateral cerebellar hæmorrhagic infarction
79902	F	52	Bilateral cerebral hæmorrhages	83612	F	58	Multiple cerebral softenings
82435	M	39	Cerebral hæmorrhage				
84237	F	59	Multiple cerebral infarcts				
85678	M	55	Cerebral hæmorrhage				

* Postmortem not performed.

When the eighth untied pair had been observed, five favoured the control treatment and three the anticoagulant treatment. The plotted path had reached the dotted line shown in the figure, indicating that a verdict in favour of anticoagulants was no longer possible with the experimental design chosen. Clearly there was no justification for continuing the trial merely to detect a significant difference in favour of control treatment should such exist, and the trial was accordingly stopped with no significant differences demonstrated. A few more results of pairs already in the trial became available with the completion of 6-week follow-up periods after the dotted line had been reached. In all, twenty-six patients were treated with anticoagulants of whom twenty survived to 6 weeks; twenty-five patients were in the control group of whom twenty-two survived to 6 weeks.

The results, including late deaths during a 6-month follow-up period, and further cerebral ischæmic episodes during treatment and follow-up, are summarised in table III. No conclusions can be drawn from this table. Postmortem examinations (Prof. William Blackwood and Dr. W. G. P. Mair) were performed on eight of the nine patients who died within the first 6 weeks, and the causes of death are shown in table IV. In the treated cases the infarcts did not differ morphologically from those normally encountered in untreated patients, and hæmorrhagic infarction was not seen; three patients died of cerebral hæmorrhage, however. Study of the case-histories of the patients who died in respect of age, blood-pressure, severity of initial lesion, and time-interval before treatment was started, did not show that the unfavourable results were confined to any particular subgroup. All eight patients with internal-carotid occlusions in both groups survived, whereas four of the seven patients diagnosed as having vertebrobasilar occlusions died—two being in the treatment group and two in the control. But no conclusions can be drawn from such small numbers. No hæmorrhagic complications of therapy arose from sites other than the central nervous system.

Discussion

This trial was undertaken in an attempt to answer a specific practical problem regarding the management of one of the commonest medical emergencies. The knowledge that anticoagulants have been reported to benefit certain groups of patients is not always helpful in planning the immediate treatment of an individual patient. Cases can be classified more easily in retrospective analysis than on the day of admission to hospital, when one may have to decide promptly whether to give anticoagulants. The retrospective formulation of the illness takes account of its total course, sometimes including necropsy findings, and it never gives a satisfactorily quantitative balance between therapeutic successes and failures, misdiagnoses, and complications of treatment. Of the patients with strokes in whom benefit from anticoagulants may be expected on the basis of reported series, only a few—such as those with insufficiency and vertebrobasilar syndromes—are clinically distinguishable in the early stages. For example, without a period of observation during which the opportunity for effective treatment may be lost, one cannot tell that a stroke is still evolving, and the majority of cases of acute carotid occlusion present a clinical picture which is indistinguishable from that associated with middle-cerebral occlusion (Silverstein 1959). The physician is therefore faced with a difficult choice. Either he must treat with anticoagulants all patients who have had a stroke and in whom there are no obvious contraindications, in the hope that an unpredictable proportion of them will benefit, or alternatively he must withhold anticoagulants knowing that he may deny a possibly effective treatment to some of his patients.

Our trial was designed in relation to these considerations; the criteria of selection of the patients were not precise, but they seemed appropriate and generally applicable to the clinical problem. According to our criteria of selection and management, even with the added refinement of cerebral angiography in all cases, we were unable to show any benefit from anticoagulant treatment. More than this cannot be inferred from the data. Although the trend of the results may suggest that anticoagulants may even be hazardous when used as in the trial, this has not been proven. Had the trial been continued the lower boundary might have been reached, showing that treatment was definitely harmful, but alternatively it might have proceeded to a point where no significant difference emerged between treatment and control groups. There was obviously no justification for continuing the trial simply to make this distinction.

Analysis of the causes of death shows that preponderance in the treatment group is attributable to the three cases of cerebral hæmorrhage These were clearly massive intracerebral extravasations, and not simply hæmorrhagic infarctions One hæmorrhagic infarction was encountered among the fatalities in the control group, but there was none in the treatment group as had been forecast The most likely explanation of why these cases of hæmorrhage were in the treatment group is that the original stroke was in fact due to hæmorrhage which was mistakenly regarded as infarction despite lumbar puncture and cerebral angiography Barron and Fergusson (1959) have drawn attention to the large number of fatal cerebral hæmorrhages among the extensive reports on anticoagulant therapy in cerebrovascular disease Therefore so long as our ability to distinguish cerebral hæmorrhage from infarction remains poor, so long will the use of anticoagulants for cerebrovascular accidents carry the risk of aggravating a misdiagnosed cerebral hæmorrhage The limitations of diagnosis in cases of stroke are further emphasised by two examples in this series despite typical presentations and normal angiograms and cerebrospinal fluid, these patients had cerebral tumours One was in the treatment group, the other in the control, both survived to 6 weeks and so did not influence the analysis

This study in no way refutes the findings of previous workers who have reported benefit from anticoagulants in limited subgroups of cerebrovascular accidents It suggests, however, that these subgroups may be difficult to recognise in the acute phase of the illness when treatment has to be initiated, and that, as a practical therapeutic measure for most patients with strokes, anticoagulants are not to be recommended A controlled trial is, we think, the only satisfactory method of assessing the value of treatments of potential hazard The sequential form of analysis is suited to such trials because it allows detection of differences at a relatively early stage

Summary

A controlled trial of anticoagulant therapy was made in fifty-one patients with a diagnosis of acute non-embolic non-hæmorrhagic cerebrovascular accident Patients were randomly allocated to treatment or control groups, and the results, measured by survival to 6 weeks, were analysed by a restricted sequential procedure The conclusion was that anticoagulants, when used according to the criteria of selection and management of the trial, are not of value

We are greatly indebted to Dr P Armitage for the detailed statistical design to suit the particular requirements of this trial, and to the Nuffield Foundation for financial support

The results of this trial were communicated at a Conference on Occlusive Vascular Disease at the Royal College of Physicians in November, 1959, the proceedings of which are to be published by the Pitman Medical Publishing Co Ltd.

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SERUM-TRIGLYCERIDE LEVELS IN SOUTH AFRICAN EUROPEANS AND BANTU AND IN ISCHÆMIC HEART-DISEASE

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Studies on the epidemiology of ischæmic heart-disease have shown a pronounced difference in the prevalence of the disease in population groups subsisting on diets of varying lipid composition In general, population groups having a high fat caloric intake (as in Western countries) tend to have a higher prevalence of the disease than groups subsisting on a low fat caloric diet, such as the South African Bantu

Most of these studies have been confined to an examination of the influence of dietary factors on serum-cholesterol levels, and relatively few reports have dealt with the manner in which fasting serum-triglyceride levels may be affected

Interest in serum-triglyceride concentrations in health and disease has been greatly stimulated since it has been shown that hyperlipæmia may not only accelerate blood-clotting (Duncan and Waldron 1949, Fullerton et al 1953, Poole 1955, O'Brien 1955, Buzina and Keys 1956, MacLagan and Billimoria 1956, MacDonald and Edgill 1957), but also increase blood-viscosity, as well as producing increased adhesiveness and aggregation of red blood-cells (Swank 1951, 1954, 1956, Cullen and Swank 1954) Close correlation has recently been shown between raised fasting-serum-triglyceride levels and the prevalence of ischæmic heart-disease by Albrink and Man (1959) Other workers (Hatch et al 1955, Albrink and Man 1956, Ahrens 1957, Havel 1957a, 1957b, Ahrens et al 1957, 1958, Dole et al 1959, Kuo and Carson 1959) have shown that variations in both the fat and carbohydrate composition of the diet may rapidly produce distinct changes in serum-triglyceride concentration, with only slight immediate effects on serum cholesterol and phospholipid levels

Accordingly we felt that valuable information might accrue from a study of fasting serum-triglyceride levels in the two main racial groups living in South Africa (1) the European, whose diet in the main is similar to that of most people of the Western hemisphere (i e , containing approximately 40% of calories derived mainly from animal fat), and among whom the prevalence of ischæmic heart-disease is high, and (2) the Bantu, whose diet in general contains less than 15% of calories from fat, is high in carbohydrate content, and among whom the prevalence of ischæmic heart-disease is very low

We describe here the findings for these two population groups subsisting on their habitual diets

Cases Studied

Those investigated were 46 healthy European males, aged 18–62 years, 23 healthy European females (18–46 years), all premenopausal, 23 European patients with ischæmic heart-disease, aged 33–67 years (2 males less than 40 years, 6 males and 3 females 41–50 years, 7 males and 2 females 51–60 years, and 3 males more than 60 years), and 57 healthy Bantu males aged 20–60 years

The healthy European subjects were active members of the technical staff of the South African Institute for Medical Research, who showed no clinical evidence of ischæmic heart-disease X-ray examination of the heart, chest, and lungs in each subject showed no abnormalities Electrocardiography was not carried out The patients with ischæmic heart-disease were at the Johannesburg General Hospital, all had been admitted on account of recent acute myocardial infarction This diagnosis was based in each case on clinical evidence and was confirmed by electrocardiography Blood samples were in each case taken during the first week after infarction These patients had received no anticoagulant therapy before this investigation was carried out The Bantu subjects consisted of mineworkers who undergo careful physical examination before being accepted for employment, and were clinically normal

In the case of the European subjects blood specimens were drawn before breakfast after an overnight fast of twelve to fourteen hours This was not possible in the case of the Bantu volunteers The Bantu mineworker has a light breakfast before starting an eight-hour shift underground without any food intake during the shift, except in some cases where a midday drink of "kaffir beer"—a non-alcoholic carbohydrate beverage—was taken All specimens of blood were drawn immediately after the day's shift had been completed and before the subjects consumed any food

Methods

Triglycerides were estimated by several methods, all of which gave close correlation A modification of the method of Van Handel and Zilversmit (1957), using activated silicic acid and isopropyl ether, was used for the initial separation of serum-triglycerides, cholesteryl esters, and free cholesterol from phospholipids, and the extracts obtained in this manner were hydrolysed by the method of Carlson and Wadstrom (1959) Liberated glycerol was then estimated fluorimetrically by the method of Mendelsohn and Antonis (1960) The phospholipid-free extracts were also analysed for ester groups by the method of Stern and Shapiro (1953), and for cholesteryl esters by the method of Schoenheimer and Sperry, as modified by Sperry and Webb (1950) Triglyceride values were then calculated by subtraction of the cholesteryl-ester content from that of total ester groups Total lipid extracts were fractionated by the silicic-acid chromatographic technique of Barron and Hanahan (1958), and triglycerides were estimated on the appropriate fractions by the above techniques, and also by hydrolysis and titration of the liberated fatty acids Since serum phospholipid and total-fatty-acid levels were also estimated on the samples (by the methods of Fiske and Subbarow [1925] and Stern and Shapiro [1953], respectively), serum-triglycerides were calculated by the method of Thannhauser and Reinstein (1942) In general, correlation was good, except in the case of some of the older normals and the patients with ischæmic heart-disease, where lower triglyceride values were obtained by calculation than were found experimentally Triglyceride polyenoic fatty acids were estimated after alkali isomerisation by the ultraviolet spectrophotometric method of Holman and Hayes (1958)

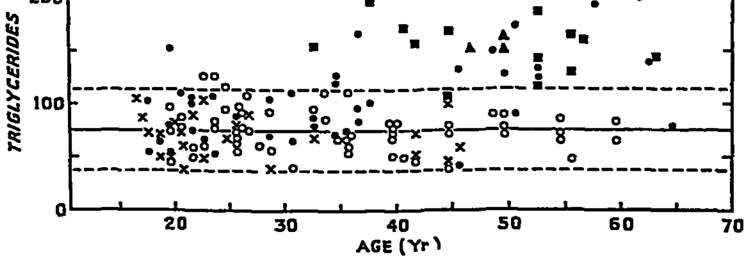

Fig 1—Fasting serum-triglyceride levels at different ages.

The continuous line represents the mean (75 mg per 100 ml), and the interrupted lines upper and lower limits of normal (mean±1 96× S.D) for the Bantu subjects at all ages (114 and 36 mg per 100 ml, respectively) Open circle represents Bantu males, closed circle, European males, cross, European females, triangle, 3 postmenopausal European females, and square, patients with ischæmic heart-disease

TABLE I—FASTING SERUM-TRIGLYCERIDE LEVELS (MG PER 100 ML.)

Age (yr)	Bantu males			European males			European females			Ischæmic heart-disease		
	No	Mean	S D	No	Mean	S.D	No	Mean	S.D	No	Mean	S.D
<30	26	80	±21	16	86	±26	18	69	±20			
31–40	16	73	±19	12	97	±28		–		M 18	197	±62
41–50	9	66	±17	7	174	±84	5	65	±20	F 5	192	±53
51–60	6	68	±12	8	174	±53						
>60				3	139	±49						
Whole group	57	75	±20				23	68	±20	23	196	±61

For Bantu males, the decrease in the mean serum-triglyceride level with age is not significant since the regression equation for age against serum-triglyceride level is not significantly different from zero (correlation coefficient 0 17)

For European males, both the means and the standard deviations of the under-40-year age-groups are significantly different from those of the 41–60-year age-groups

The mean for the cases of ischæmic heart-disease is not significantly different from that of the 41–60-year European males

Results

Serum-triglyceride Concentration

Individual fasting serum-triglyceride levels for the 152 subjects investigated are shown according to age in fig 1

The majority of the young subjects of both races and sexes have values of under 114 mg per 100 ml, shown by the upper interrupted line This value has been calculated from the results obtained for the Bantu subjects as the mean+1 96×S D Only 2 5% of these subjects will therefore be expected to have serum-triglyceride levels above this value Comparison of the serum-triglyceride levels for the other groups shows that all the European premenopausal females have triglyceride levels lying below this value, in the case of the European males, 6% of the under-30, 25% of the 31–40, 86% of the 41–50, and 88% of the over-50 age-groups, as well as over 96% of the heart-disease cases, had serum-triglyceride concentrations greater than 114 mg per 100 ml

Serum-triglyceride levels of Bantu males and European females (premenopausal) show no age trend Values for European males, however, show a distinct age trend with a widening scatter Ischæmic-heart-disease patients at all ages have serum-triglyceride levels very much higher than those of young subjects, but only slightly higher than a large proportion of the older European males, and no age trend is apparent. These results have been examined statistically, and the mean value for each group of subjects divided by decade, is shown in table I

For Bantu males the mean serum-triglyceride level decreases slightly from age 20 years through to age 50 years, but this fall is not significant since the regression on age gives a correlation coefficient (0 17) not significantly different from zero Since the standard deviations for the various decades are also not significantly different, the Bantu group can be considered homogeneous with a mean serum-triglyceride level of 75±20 mg per100 ml

European females (premenopausal) under 46 years of age show no age trend, and have a mean serum-triglyceride

TABLE II—TRIGLYCERIDE POLYENOIC-FATTY-ACID COMPOSITION (MEAN ± S D)

Group	No	Total fatty acids (mg per 100 ml)	Percentage of total fatty acids				
			Dienoic	Trienoic	Tetraenoic	Pentaenoic	Hexaenoic
European females <46 yr	13	74±19	27·1±3·2	6·4±0·8	5·9±1·1	1·5±0·3	3·9±0·9
Bantu males all ages	57	71±19	30·7±2·1	6·9±1·5	8·3±2·8	2·7±0·7	5·8±1·5
European males 18–30 yr	8	72±21	26·6±1·6	6·5±1·3	5·5±1·0	1·7±0·5	3·9±1·5
European males 31–40 yr	8	86±18	21·7±4·5	5·6±1·1	5·5±1·5	1·9±0·6	4·2±1·6
European males 41–70 yr	13	186±55	20·2±3·6	4·0±1·4	5·8±1·8	1·9±0·7	4·9±1·3
Patients with ischæmic heart-disease, all ages, both sexes	23	188±58	18·1±2·5	3·2±1·0	4·0±1·4	1·0±0·7	4·1±1·8

Bantu mean serum-triglyceride dienoic, tetraenoic, and hexaenoic fatty-acid percentages are significantly greater than those of European males under 30 years of age ($P<0·001$, $P<0·01$, and $P<0·01$, respectively)

European males under 30 years and European females under 46 years of age have polyenoic-fatty-acid patterns not significantly different from each other Their mean serum-triglyceride dienoic-fatty-acid percentage is significantly greater than that of European males over 30 years of age and ischæmic-heart-disease cases ($0·01<P<0·02$)

level of 68±20 mg per 100 ml 3 European females over age 46 years, all postmenopausal, had higher levels—150 mg , 150 mg , and 158 mg , per 100 ml

European males under 30 years of age have a mean serum-triglyceride level of 86±26 mg per 100 ml , not significantly different from the values of the Bantu and European females For the 31–40-year group the corresponding mean is 97±28 mg per 100 ml After this decade, however, there is a clear upward trend, and the means for the next two decades are 174±84 mg and 174±53 mg per 100 ml , respectively Ischæmic-heart-disease patients whose ages ranged from 33 to over 60 years had higher serum-triglyceride levels than all the other subjects, but no age trend was apparent in the few cases investigated The mean for this group was 196±61 mg per 100 ml

The standard deviations of the 31–40 and 41–50 year European male groups are significantly different at less than the 2% level (variance ratio=9·55, 2%=7·72) Fig 2 shows the means and the 95% confidence interval of the means plotted decade by decade for the Bantu and European males For the European males, both the means and the standard deviations increase significantly with age

Means are significantly different where no overlapping occurs of the 95% confidence limits, as depicted by the interrupted lines Standard " t " test or regression analysis is not relevant because of the significant difference in the standard deviations (Kendall 1951)

The figure also clearly shows that the Bantu mean is significantly different from those of the European male groups over the age of 30 years

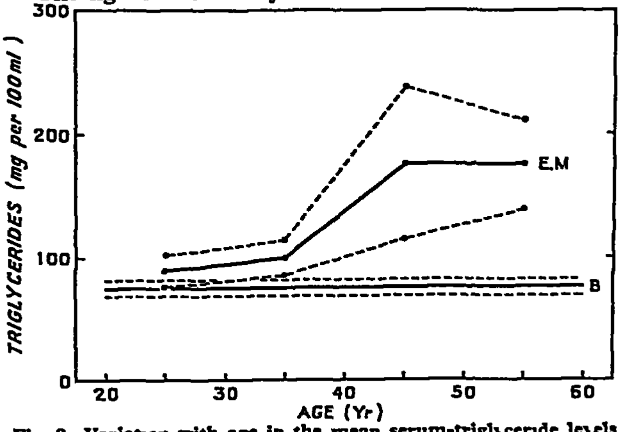

Fig 2—Variation with age in the mean serum-triglyceride levels of European and Bantu male subjects.

The lower continuous line represents the means for the Bantu subjects of all ages, and the interrupted lines on each side represent the 95% confidence limits of the means $\left(1·96 \times \sqrt{\frac{\text{variance}}{N}}\right)$ The upper continuous line represents the means, and the interrupted lines on each side represent the 95% confidence limits of the means, for the European male subjects through the decades 20–60 years Means are significantly different where the 95% confidence limits do not overlap

The mean value for the ischæmic-heart-disease cases was higher than those of the European males aged 41–50 and 51–60, but the differences were not statistically significant.

The frequency distribution of the serum-triglyceride concentration for the four groups—Bantu, European males under 40 years, European males over 40 years, and ischæmic-heart-disease cases—is compared in fig 3

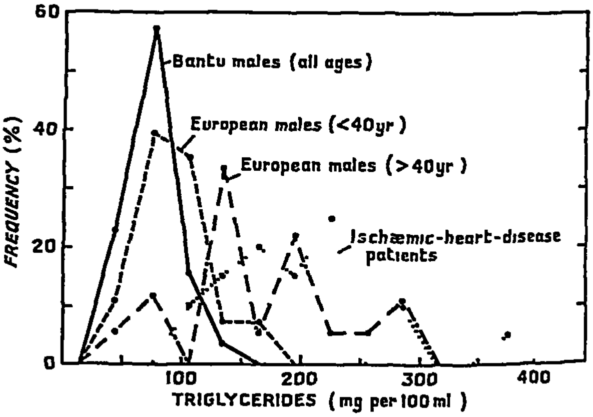

Fig 3—Frequency distribution of serum-triglycerides

For all the Bantu and the younger European subjects, the greatest frequency of the distribution lies between triglyceride levels of 30 and 130 mg per 100 ml and is of the " normal " type Although just under 50% of the older European subjects and 25% of the heart-disease cases have serum-triglyceride levels within this range, the greater frequency distribution of these groups is at levels well over 150 mg per 100 ml The frequency distribution of the European female values (not shown in the figure) is almost identical with that of the Bantu

Serum-triglyceride Polyenoic-fatty-acid Composition

The mean polyenoic-fatty-acid patterns of the subjects already described are shown in table II Comparison of the pattern for the Bantu with those of the other subjects shows several differences

As was the case for absolute serum-triglyceride levels, the polyenoic-fatty-acid distribution for Bantu, female Europeans, and heart-disease cases shows no variation with age, and the groups are considered homogeneous for statistical analysis For male Europeans, however, a considerable inverse variation with age is shown in the percentage of dienoic fatty acids (linoleic acid)—thus decreasing with increasing age No significant changes are apparent for the more highly unsaturated polyenoic fatty acids Ischæmic-heart-disease cases have a lower proportion of all polyenoic fatty acids in their serum triglycerides than the other subjects

Bantu serum-triglycerides have significantly greater proportions of dienoic, tetraenoic, and hexaenoic fatty acids than the corresponding serum-triglycerides of all the other groups In comparison with European males under 30 years, values for P are less than 0 001, 0 01, and 0 01, respectively European males under 30 years, and females under 46 years have triglyceride polyenoic-fatty-acid patterns not significantly different from each other, but both these patterns differ significantly in their dienoic-acid content from those of European males over 30 years and ischæmic-heart-disease cases (0 01 < P < 0 02)

Discussion

The statistical analysis of the age variation of the absolute serum-triglyceride levels of the European males reveals important aspects Since not only the means for the different age-groups but also the standard deviations show significant variation, it seems apparent that the population is not homogeneous, and that different sections show different age trends The under-30-year and the 31–40-year groups show only slight variation in the standard deviations of their mean serum-triglyceride concentration For the older groups, however, the large and significant increase of the standard deviation suggests that there may be a mixture of two populations—one sample representing the true normals and showing a standard deviation possibly of the same order as the younger males, and a second sample representing subjects with a higher mean The mean samples from the over-40-year groups would in this case be expected to show a biphasic frequency distribution Although there is some indication that this may be the case (see fig 3), the number of subjects investigated was too small to allow any firm conclusions to be drawn

Since the mean level for the ischæmic-heart-disease patients was only slightly higher than that of the older European males, the implication could be that the older overtly normal population consists of a mixture of the true normals with a large proportion of subjects biochemically indistinguishable from ischæmic-heart-disease cases These latter subjects may therefore represent potential cases of ischæmic heart-disease, and high serum-triglyceride levels may thus be predictive of future vascular disease On the other hand the entire European male population as it ages may have a rising serum-triglyceride level without any distinct break between normals and abnormals, but in that event the rate of increase is not constant, the level rising more rapidly in some than in others

Similar conclusions were reached by Albrink and Man (1959) in their study of an American population. They found that fasting serum-triglyceride levels exceeded 160 mg per 100 ml in only 5% of normal young adults, in 30% of normal men over 50 years, and in 90% of patients with ischæmic heart-disease Our own study indicates a very much lower value for the upper limit of normal (114 mg per 100 ml), since 94% of the young European males, 97 5% of the Bantu males, and all the young European females have serum-triglyceride levels below this value. Possible objections to the use of the Bantu upper limit for both racial groups, on the grounds, firstly, of race difference and, secondly, that Bantu high-carbohydrate, low-fat dietary habits are very different from those of the European population, would not appear to be valid, since our own studies on a prison population (to be published shortly) have confirmed that both older European (aged 31–40 years) and Bantu prisoners who have subsisted for long periods on a prison diet almost identical in composition with that consumed by the urban Bantu population, have serum-triglyceride levels falling well within the upper limit of 114 mg per 100 ml In a given population irrespective of race, therefore, habituation to high-carbohydrate, low-fat calorie diets does not appear to lead to raised serum-triglyceride levels

The Bantu and European subjects differed in their preparation in that the former were investigated after a day's work, but the influence of exercise on the fasting triglyceride levels, particularly in younger subjects, does not seem to be important since both the Bantu and European prisoners mentioned above had fasting levels, after a night's rest, not significantly different from those of the Bantu mineworkers (For 26 European prisoners the mean was 83±23, range 37–118, mg per 100 ml, and for 19 Bantu prisoners the mean was 86±25 mg, range 46–121, mg per 100 ml, with the exception of 1 Bantu volunteer whose fasting level varied between 136 and 158 mg per 100 ml)

It is nevertheless important, in evaluating serum-triglyceride levels, to consider the previous dietary history of the subjects, since restriction of dietary fat intake with isocaloric substitution by carbohydrate produces at once temporarily much-elevated triglyceride levels (Havel 1957a, 1957b, Albrink and Man 1956, Hatch et al 1955, Ahrens et al 1957, Ahrens 1957a, Ahrens et al 1958, Kuo and Carson 1959, Dole et al 1959) This could lead to incorrect interpretation of the basal fasting serum-triglyceride levels of individuals, especially since these raised levels appear to subside very slowly

Comparison of the triglyceride levels with their polyenoic-fatty-acid composition indicates that raised levels are associated with a lowered proportion of dienoic acids In the case of the Bantu the low serum-triglyceride levels are associated with significantly raised proportions of dienoic, tetraenoic, and hexaenoic fatty acids Whether this finding represents a different fat metabolism in Bantu to that in the European subjects, or whether it is of dietary origin, is not clear Recent studies by Ahrens et al (1959), and by Dole et al (1959) suggest that both factors are important Ahrens et al (1959) have shown that the composition of the serum-triglyceride fatty acids strikingly resembles the composition of the dietary fat, and we have confirmed this in our own studies Dole et al (1959), on the other hand, have shown that the immediate changes in serum-triglyceride fatty-acid composition produced by fat loading are slight, and have suggested that the fatty-acid pattern is more dependent on that of tissue-lipids Since the composition of the latter, however, is also known to change gradually with the nature of the dietary fat over a long period, it seems that the changes in serum-triglyceride fatty-acid composition are secondary and depend on metabolic processes involving utilisation of depot fat

The diet of the Bantu subjects is low in fat, but this is rich in linoleic acid, which has been shown to be a precursor for arachidonic and hexaenoic fatty-acid synthesis This may partly account for the higher proportion of these polyenoic acids in the serum-triglycerides of the Bantu subjects than in those of the European subjects

On the other hand, the diet of the European subjects in the present study is similar both in intake and in nature of the dietary fat (mainly saturated) The nature of the dietary fat therefore does not in this instance appear to be the only f[illegible]encing the composition of the tri-

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glyceride fatty acids, and the qualitative and quantitative variation of the serum-triglycerides in the European subjects may indicate a fundamental change in the triglyceride metabolism of the older European male compared with that of the younger European male and female and Bantu subjects This change may be due to faults in fat transport and clearing mechanisms either produced or aggravated by excessive intake of dietary fats rich in saturated fatty acids In view of the widely differing incidence of ischæmic heart-disease among these subjects—rare in the Bantu but becoming increasingly prevalent among younger European males—it would appear that ischæmic heart-disease, which is associated with raised serum-triglyceride levels, may also be largely due to faulty triglyceride metabolism brought about by habitual consumption of diets rich in saturated fat

Long-term studies of triglyceride metabolism on normal subjects subsisting on such diets would give a clearer indication as to whether this possibly explains the raised serum-triglyceride levels of the older male population and the patients with heart-disease

The influence of sex on serum-triglyceride composition and concentration are also apparently important since all the premenopausal females had low triglyceride levels This corresponds to the lower prevalence of ischæmic heart-disease in premenopausal than in postmenopausal women

Summary

The concentration and polyenoic-fatty-acid composition of serum-triglycerides has been estimated in 152 South African European and Bantu subjects, and in patients with ischæmic heart-disease

Young European males, premenopausal European females, and Bantu males of all ages have similar, low, serum-triglyceride levels

European males over 40 years of age, and patients with ischæmic heart-disease of all ages and each sex, have raised serum-triglyceride levels

In European males a clear age trend is evident both in the polyenoic-fatty-acid composition and in the concentration of the serum-triglycerides It is suggested that the older European male population consists of a mixture of " normals " and potential cases of ischæmic heart-disease, and that these two groups can possibly be distinguished by the serum-triglyceride levels

We thank the Director of the South African Institute for Medical Research for his interest in this study, Miss C D Sussman, B Sc, Miss C Cavedoni, Miss E Klinck, Mrs A Isaacs, and Mr E du Toit, B Sc, for technical and other assistance, Dr A M Adelstein for statistical analysis, and the volunteers who made this study possible

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WEIGHT-LOSS IN PERNICIOUS ANÆMIA

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Thomas Addison, in his classical description of pernicious anæmia (1855), emphasised that patients with this disease remain obese Today, the clinical impression is generally held that such patients do not lose weight, although there have been a few reports that some do

Thus, Jones (1938) observed weight-loss in 42 of 78 patients with pernicious anæmia, while Read and Asher (1956) found weight-loss of over one stone in 14 out of 50 patients On the other hand, Davis and Brown (1953) considered weight-loss to be rare in uncomplicated pernicious anæmia, and Girdwood and Innes (1958) note that these patients generally appeared well nourished

When weight-loss is associated with alimentary symptoms the most likely diagnosis is often thought to be gastric carcinoma, although, in our experience, this combination of symptoms is not uncommon in pernicious anæmia Consequently the simple diagnostic procedures which confirm the diagnosis of pernicious anæmia have sometimes been delayed, and in a few cases unnecessary laparotomies have been carried out We therefore studied 50 cases of pernicious anæmia and 50 cases of gastric carcinoma in order to compare the clinical patterns of these two conditions We were able to confirm that weight-loss occurred in a significant proportion of cases of pernicious anæmia Since vitamin B_{12} is now known to influence the metabolism of many tissues besides blood we attempted at the same time to find out which tissues were mainly affected by the weight-loss associated with vitamin-B_{12} deprivation

Materials and Methods

The 50 cases of pernicious anæmia and 50 cases of gastric carcinoma were admitted to the Western Infirmary in the two-year period 1957–58 The diagnosis of gastric carcinoma was accepted on the basis of laparotomy with biopsy and histological evidence The criteria for acceptance of a diagnosis of pernicious anæmia were macrocytic anæmia, megaloblastic erythropoiesis in the bone-marrow, histamine-fast achlorhydria (Kay 1953), and a reticulocyte response of over 10% after treatment with vitamin B_{12}

In 11 patients in whom we investigated weight-loss and red-blood-cell volume, serum-vitamin-B_{12} levels or vitamin-

TABLE I—INCIDENCE OF PRINCIPAL CLINICAL FEATURES IN 50 CASES OF PERNICIOUS ANÆMIA AND 50 CASES OF GASTRIC CARCINOMA

Clinical features	Percentage of cases	
	Pernicious anæmia	Gastric carcinoma
Lack of energy	100	50
Pallor	100	54
Dyspnœa	76	24
Abdominal or dyspeptic symptoms	54	94
Anorexia	44	70
Loss of weight	36	42

B_{12}-absorption tests or both were done. In these 11 patients estimations of antipyrine space, thiocyanate space, and plasma-volume (Evans-blue) were carried out before treatment and at least three months later by the methods described by Muldowney (1957). It was found that within three months the blood values and the weights of the patients had been restored to their normal levels. "Lean body mass" was calculated from the antipyrine space by the equation of Pace and Rathbun (1945) and in addition by the Keys-Brozek formula (Keys and Brozek 1953), which takes into account the extracellular fluid as deduced from the thiocyanate space.

Results

Lack of energy, pallor, and dyspnœa were the commonest features of pernicious anæmia, while abdominal or dyspeptic symptoms, anorexia, and loss of weight were the commonest in gastric carcinoma (table I).

We have described epigastric pain or discomfort, heartburn, sour mouthfuls, flatulence, nausea, vomiting, or diarrhœa as "abdominal or dyspeptic symptoms". "Loss of weight" indicates an estimated weight-loss of 14 lb. or more in the year preceding diagnosis. 36% of our patients with pernicious anæmia had a weight-loss of 14 lb. or more. The results of analysis of some laboratory investigations are recorded in table II. Anæmia in gastric carcinoma can be as severe as that in pernicious anæmia, but is not usually so. The erythrocyte-sedimentation rate (Westergren) varied from normal to much increased in each disease. On the other hand the fæcal occult-blood test was positive in only 4 of 37 cases of pernicious anæmia but was positive in 9 out of 12 cases of gastric carcinoma so tested. Histamine-fast achlorhydria was found in all cases tested in each disease, but only 13 such investigations were recorded in the cases of gastric carcinoma. Clearly there is much overlap in the clinical features of these two diseases, which may explain the fact that 11 patients (22%) with pernicious anæmia were initially suspected of having gastric carcinoma. 5 were referred initially to surgeons because of severe alimentary symptoms associated with weight-loss, and 3 of these were admitted to surgical wards; 1 patient was further investigated by means of gastroscopy. Physicians made the initial diagnosis of gastric carcinoma in 6 cases which were later shown to be of pernicious anæmia; in each of these cases weight-loss was a prominent clinical feature.

TABLE II—RESULTS OF LABORATORY INVESTIGATIONS IN PERNICIOUS ANÆMIA AND GASTRIC CARCINOMA (NUMBER OF CASES INVESTIGATED SHOWN IN PARENTHESES)

—	Pernicious anæmia	Gastric carcinoma
Hb (%)		
Range	23–66 (50)	26–107 (32)
Mean and S.D.	44±11 (50)	70±19 (32)
E.S.R.	5–116 (37)	4–45 (22)
F.O.B. positive	4 (37)	9 (12)
H.F.A.	50 (50)	13 (13)

Hæmoglobin (Hb) 100% = 14·8 g. per 100 ml.
S.D. = standard deviation.
E.S.R. = erythrocyte-sedimentation rate (Westergren) mm. in first hour.
F.O.B. = fæcal occult blood.
H.F.A. = histamine-fast achlorhydria.

Muldowney (1957) showed that for normal people the red-blood-cell volume did not closely correlate with the total body-weight. He did find, however, close correlation between red-cell volume and "lean body mass" in normal people, and the linear regression of red-cell volume (y) on "lean body mass" (x) was found to be $y = 32{\cdot}7x - 155{\cdot}17$. In our patients with untreated pernicious anæmia the (product moment) coefficient of correlation between red-cell volume and total body-weight was $-0{\cdot}41$, which is not significantly different from zero; in treated cases the coefficient of correlation was $+0{\cdot}61$ which is significantly different from zero ($P < 0{\cdot}05$). In our 11 untreated cases of pernicious anæmia the correlation coefficient between red-cell volume and "lean body mass" was $-0{\cdot}36$, which is not significantly different from zero. For the treated state the corresponding coefficient of correlation was $-0{\cdot}92$, which is significantly different from zero ($P < 0{\cdot}01$). This is illustrated in fig. 1. The linear regression of red-cell volume (y) on "lean body mass" (x) was found to be $y = 31{\cdot}70x + 277{\cdot}3$. The regression coefficient (31·70) agrees very satisfactorily with Muldowney's value of 32·74.

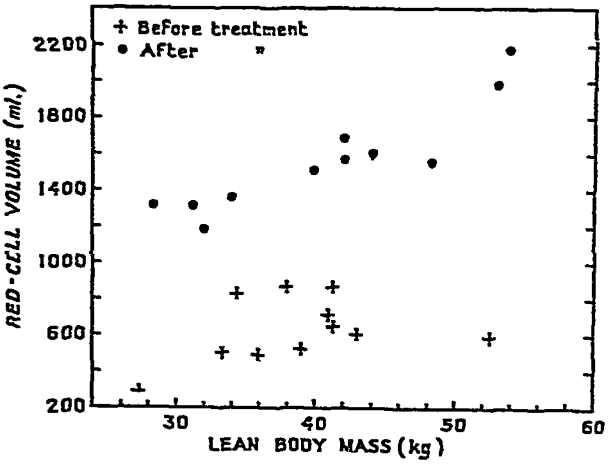

Fig. 1—Scatter diagram of red-cell volume and "lean body mass" in patients with pernicious anæmia before and after treatment.

The gain in weight of these 11 patients after the restoration of normal blood-levels varied from under 5 kg. to over 15 kg. The measurement of "lean body mass" allowed us to estimate that proportion of weight gain due to fat and that due to lean tissue (table III). The estimation of "lean body mass" derived from the antipyrine space by the Pace-Rathbun equation was compared with that derived from the Keys-Brozek formula which incorporates a correction for extracellular-fluid changes. The mean difference between the two estimations (Pace-Rathbun minus Keys-Brozek) for the 11 untreated patients was only +0·06 kg., and for the patients after treatment it was only −0·12 kg. This suggests that the estimations of "lean body mass" were valid despite the possibility of subclinical œdema in untreated patients with pernicious anæmia. In only 1 of these patients (case 4) was there any evidence of clinical œdema, and this was mild. In this patient the measurement of extracellular fluid by thiocyanate was significantly

FLACCID QUADRIPLEGIA FOLLOWING URETERIC TRANSPLANT

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Anastomosis of the ureter to the colon often produces metabolic abnormalities (Wilkinson 1954, Milne 1957) These were present in 80% of patients a year after operation (Ferris and Odel 1950), and consisted of a raised blood-urea and plasma-chloride with a lowered plasma-bicarbonate Significant hypokalæmia has been reported in 35% of cases (Jacobs and Stirling 1952), occasionally being severe (Parsons et al 1952, Wilkinson 1952) These biochemical abnormalities did not invariably cause symptoms, if present these consisted of tiredness, weakness, anorexia, nausea and vomiting, a salty taste in the mouth, and thirst and consequent polyuria (Milne 1957)

Hypokalæmia has been associated with muscular weakness (Foster et al 1950, Matern 1954), and Diefenbach et al (1951), Skanse and Widén (1955), and Loughlin (1956) have described cases in which flaccid quadriplegia developed, as in the case reported here

DATA ON BLOOD CHEMISTRY IN THE FIRST FOUR DAYS AFTER ADMISSION AND SIX MONTHS LATER

—	Oct 7, 1958	Oct. 8, 1958	Oct 9, 1958	Oct 10, 1958	April 6, 1959
Plasma-sodium (mEq per litre)	135	143	139	144	142
Plasma-potassium (mEq per litre)	1-5	2 8	3 5	4 5	4 2
Plasma-chloride (mEq per litre)	114	100	95	98	111
Plasma alkali reserve (mM per litre)	12	23	33	37	17
Blood-urea (mg per 100 ml)	100	70	45	45	80

Case-report

A male clerk, aged 25, was admitted to hospital on Oct 6, 1958, with a provisional diagnosis of acute poliomyelitis For some days he had felt thirsty, with a dry throat, and two days previously he had felt tired after a strenuous game of football, the next day he had felt weak and noticed " a heaviness in the legs " On the day of admission he found it impossible to go to work owing to weakness of his arms and legs, and that evening he was found to have severe weakness of the proximal muscle-groups of all four limbs The reflexes were all present and sensation was normal His temperature was 98 4°F, pulse-rate 70 per minute, respiration-rate 20 per minute During the night he vomited repeatedly, and when seen the following morning he was dehydrated and clinically uræmic. The paralysis had progressed, he was unable to move any of his limbs, nor could he raise his head from the pillow Respiration was rapid and shallow, and he could count only to ten in one breath

There was a past history of left-sided nephrectomy in 1946, on account of renal tuberculosis In 1949 the right ureter was transplanted into the sigmoid colon owing to pronounced frequency of micturition, the bladder capacity being only 2 oz Since the last operation he had been continent of urine and normally emptied his bowel every three hours About eight years previously he had had an attack of weakness of the limbs lasting several days which was associated with vomiting and constipation, and which responded to the administration of purgatives In April, 1957, he was treated in hospital for an attack of acute pyelonephritis, and subsequently intravenous pyelography showed a satisfactorily functioning large right kidney with slight dilatation of the calyces Apart from these episodes he had remained generally well and played football regularly at the weekends

Flaccid quadriplegia due to hypokalæmia was diagnosed clinically Estimation of plasma-electrolytes (see table) revealed a plasma-potassium of 1 5 mEq per litre Electrocardiography (see figure) showed the changes of severe hypokalæmia (Surawicz et al 1957) The hæmoglobin was 132% (19 6 g per 100 ml), packed-cell volume 57%, white blood-cells 15,000 per c.mm (polymorphs 90%)

Treatment and Progress

Intravenous therapy was started, and during the next twenty-four hours the patient received 3 litres of a solution containing 0 18% sodium chloride, 4 3% dextrose, and 0 1% potassium chloride and 3 litres of 1 87% sodium lactate In addition he was able to take copious fluids by mouth and mist pot cit *B.P C* $^1/_2$ oz four-hourly A rectal tube was inserted so that urine could be drained off continuously, and intramuscular streptomycin g 1 b d was given for the next five days in case of urinary infection

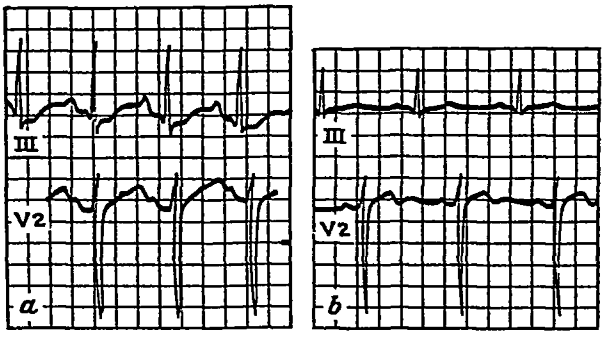
By the next morning the patient's condition was greatly improved He was obviously less dehydrated and could move his arms and legs, but he was still unable to raise his head from the pillow The blood chemistry showed improvement (see table, Oct 8) Intravenous therapy was stopped, but mist pot cit *B P C* and fluids were continued by mouth, salt being restricted The rectal drainage tube was removed after forty-eight hours He continued to improve symptomatically, and the plasma-potassium rose progressively to 4 5 mEq per litre on Oct. 10 (see table) The electrocardiogram had become normal (see figure, *b*)

The patient was discharged from hospital on Oct 14, 1958, feeling very well and taking a normal diet with no salt restriction He was given mist pot cit. *B.P C* $^1/_2$ oz b d and was advised to increase the dosage if any muscular weakness developed He was instructed to pass urine at intervals of not more than three hours Since discharge he has attended as an outpatient. He has remained well, playing football at weekends, and continues on potassium citrate regularly

The latest blood-chemistry findings (April 6, 1959) showed hyperchloræmic acidosis with raised blood-urea but normal potassium (see table)

Discussion

After ureterosigmoidostomy reabsorption of urea from the urine in the bowel results in a raised blood-urea which does not necessarily imply renal dysfunction Similarly, reabsorption of chloride ions by the colon preferentially to sodium ions accounts for the hyperchloræmic acidosis (Parsons et al 1952) Electrolyte disturbances are more severe when the ureters are transplanted into the cæcum



Electrocardiograms (leads III and V_2): *a*, Oct 7, 1958, showing sinus rhythm, PR interval 0 20 sec., QRS 0 12 sec., tall tilted P waves depressed ST segments, marked U waves which are taller than T waves in V_2 (plasma-potassium 1 5 mEq per litre), *b*, Oct 9, 1958, normal appearance, with sinus rhythm, PR interval 0 18 sec., QRS 0 1 sec. (plasma-potassium 3 5 mEq per litre)

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TABLE III—COMPARISON OF WEIGHT, "LEAN BODY MASS" (L B M) TOTAL FAT, RED-CELL VOLUME, AND THIOCYANATE (EXTRA CELLULAR-FLUID) SPACE IN 11 CASES OF PERNICIOUS ANÆMIA, BEFORE AND AFTER TREATMENT WITH VITAMIN B_{12}

Case no	Body-weight (kg)		Pace-Rathbun				Keys-Brozek				Red-cell vol (ml.)		Thiocyanate space (litres)	
			L B.M (kg)		Fat (kg)		L.B.M (kg)		Fat (kg)					
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	75 0	87 7	52 4	53 9	22 6	33 8	52 89	54 55	22 11	32 15	590	2166	17 50	17 70
2	65 9	69 5	41 2	41 8	24 7	27 7	42 32	42 86	23 08	26 64	656	1695	12·00	12 20
3	44 9	56 8	27 2	28 4	17 7	28 4	26 87	29 28	18 03	26 52	283	1308	10 75	8 70
4	63 6	70 0	37 9	33 8	25 7	36 2	35 57	32 36	27 43	37 64	867	1374	19 60	12 88
5	61 4	67 3	34 4	31 3	27 0	36 0	32 80	28 90	28 60	38 40	817	1300	11 40	12 00
6	50 9	54 1	33 3	32 2	17 6	21 9	33 57	31 96	17 32	22 14	508	1169	11 20	12 10
7	51 8	67 3	36 2	39 5	15 6	27 8	36 47	39 60	15 33	27 70	497	1517	12 30	13·90
8	52 7	66 4	43 0	52 9	9 7	13 5	42 61	52 72	10 09	13 68	612	1999	16 40	19·40
9	45 0	48 6	41 0	43 9	4 0	4 7	41 63	44 17	3 37	3 43	704	1560	13 10	12 50
10	45 0	59 5	38 9	41 9	6 1	17 6	39 76	42 66	5 24	16 84	520	1578	11 75	13 12
11	53 6	63 2	41 2	48 2	12 4	15 0	41 41	49 85	12 19	13 35	863	1580	14 32	13 10

changed following treatment with vitamin B_{12} From these studies it would appear that the fatter patients gained either wholly or mainly fat, while the lean patients gained predominantly lean tissue (fig 2)

Discussion

The results of our clinical analysis have indicated the many features which are shared by pernicious anæmia and gastric carcinoma Unless it is appreciated that a patient with pernicious anæmia may have considerable loss of weight, dyspeptic symptoms, an increased erythrocyte-sedimentation rate, and more rarely a positive test for fæcal occult blood, much effort may be misdirected and much time lost in coming to the correct diagnosis The increased incidence of gastric carcinoma in patients with pernicious anæmia (Mosbech and Videbach 1950) must not be forgotten Nevertheless, if further investigations are necessary to eliminate this possibility, these can be carried out after the patient has been treated

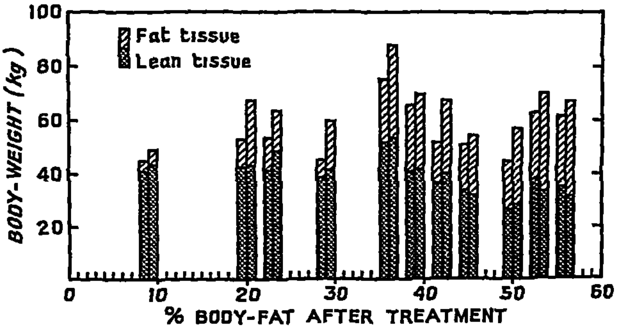

Fig 2—Proportions of fat and lean tissue in 11 patients with pernicious anæmia

Each two adjacent columns represent these tissue proportions in a patient before treatment (left column) and after treatment (right column) The columns are placed on the abscissa according to their approximate body-fat content after treatment

The highly significant coefficient of correlation (+0 92) between red-cell volume and "lean body mass" found in treated patients has confirmed Muldowney's results in normal subjects The estimations of weight-gain after treatment demonstrated a predominant accumulation of fat in obese patients and an accumulation mainly of lean tissue in lean patients In general, all these patients returned to their usual weight, and so it can reasonably be assumed that the measurements of lean and fat tissue gained were, in fact, indicative of the proportions of these tissues lost as a result of vitamin-B_{12} deprivation Vitamin B_{12} has been shown to influence the metabolism of protein, nucleic acids, carbohydrate, and fat (Arnstein 1955) in addition to its well-known effect on blood and nervous tissue

In pernicious anæmia the dramatic clinical feature is usually a diminution of circulating hæmoglobin The more subtle changes in other tissues become apparent soon after treatment is initiated by the patient's remarkable feeling of well-being long before the mass of circulating hæmoglobin is significantly altered. Weight-loss *is another manifestation of this tissue dependence* on vitamin B_{12} Although some of this weight-loss can be attributed to anorexia, a more direct cause may be the depletion of vitamin B_{12} throughout the tissues of the body

Summary

Of 50 consecutive cases of pernicious anæmia admitted to the Western Infirmary, Glasgow, 18 (36%) had an estimated weight-loss of at least 14 lb over a period of less than a year preceding diagnosis

In cases with weight-loss and alimentary symptoms, the diagnosis may be confused with that of gastric carcinoma For this reason the main clinical features of 50 cases of gastric carcinoma were compared with those of the 50 cases of pernicious anæmia There is considerable overlap of these features in the two diseases

11 patients with pernicious anæmia who had lost weight had the "lean body mass" estimated before and after treatment These studies showed that, whereas obese patients tend to lose fat and lean patients lean tissue, both may be lost in some cases

The normal correlation between red-cell volume and lean body mass is greatly disturbed in the untreated state, but is restored after treatment

We are grateful to Prof. E J Wayne and Dr J A W McCluskie in whose wards we carried out these studies, to physicians and surgeons in the Western Infirmary, Glasgow, who allowed us access to their case-records, to Miss E Macdonald, B SC, who performed the estimations of antipyrine and thiocyanate, to Dr R. A Robb, Mitchell lecturer in statistics, University of Glasgow, for the statistical analysis, and to Dr J F Adams who kindly carried out the serum-vitamin-B_{12} assays and the vitamin-B_{12}-absorption tests

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FLACCID QUADRIPLEGIA FOLLOWING URETERIC TRANSPLANT

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Anastomosis of the ureter to the colon often produces metabolic abnormalities (Wilkinson 1954, Milne 1957) These were present in 80% of patients a year after operation (Ferris and Odel 1950), and consisted of a raised blood-urea and plasma-chloride with a lowered plasma-bicarbonate Significant hypokalæmia has been reported in 35% of cases (Jacobs and Stirling 1952), occasionally being severe (Parsons et al 1952, Wilkinson 1952) These biochemical abnormalities did not invariably cause symptoms, if present these consisted of tiredness, weakness, anorexia, nausea and vomiting, a salty taste in the mouth, and thirst and consequent polyuria (Milne 1957)

Hypokalæmia has been associated with muscular weakness (Foster et al 1950, Matern 1954), and Diefenbach et al (1951), Skanse and Widen (1955), and Loughlin (1956) have described cases in which flaccid quadriplegia developed, as in the case reported here

DATA ON BLOOD CHEMISTRY IN THE FIRST FOUR DAYS AFTER ADMISSION AND SIX MONTHS LATER

—	Oct. 7, 1958	Oct. 8, 1958	Oct. 9, 1958	Oct 10, 1958	April 6, 1959
Plasma-sodium (mEq per litre)	135	143	139	144	142
Plasma-potassium (mEq per litre)	1·5	2 8	3 5	4 5	4 2
Plasma-chloride (mEq per litre)	114	100	95	95	111
Plasma alkali reserve (mM per litre)	12	23	33	37	17
Blood-urea (mg per 100 ml.)	100	70	45	45	80

Case-report

A male clerk, aged 25, was admitted to hospital on Oct. 6, 1958, with a provisional diagnosis of acute poliomyelitis For some days he had felt thirsty, with a dry throat, and two days previously he had felt tired after a strenuous game of football, the next day he had felt weak and noticed " a heaviness in the legs " On the day of admission he found it impossible to go to work owing to weakness of his arms and legs, and that evening he was found to have severe weakness of the proximal muscle-groups of all four limbs The reflexes were all present and sensation was normal His temperature was 98 4°F, pulse-rate 70 per minute, respiration-rate 20 per minute During the night he vomited repeatedly, and when seen the following morning he was dehydrated and clinically uræmic The paralysis had progressed, he was unable to move any of his limbs, nor could he raise his head from the pillow Respiration was rapid and shallow, and he could count only to ten in one breath

There was a past history of left-sided nephrectomy in 1946, on account of renal tuberculosis In 1949 the right ureter was transplanted into the sigmoid colon owing to pronounced frequency of micturition, the bladder capacity being only 2 oz Since the last operation he had been continent of urine and normally emptied his bowel every three hours About eight years previously he had had an attack of weakness of the limbs lasting several days which was associated with vomiting and constipation, and which responded to the administration of purgatives In April, 1957, he was treated in hospital for an attack of acute pyelonephritis, and subsequently intravenous pyelography showed a satisfactorily functioning large right kidney with slight dilatation of the calyces Apart from these episodes he had remained generally well and played football regularly at the weekends

Flaccid quadriplegia due to hypokalæmia was diagnosed clinically Estimation of plasma-electrolytes (see table) revealed a plasma-potassium of 1 5 mEq per litre Electrocardiography (see figure) showed the changes of severe hypokalæmia (Surawicz et al 1957) The hæmoglobin was 132% (19 6 g per 100 ml), packed-cell volume 57%, white blood-cells 15,000 per c.mm (polymorphs 90%)

Treatment and Progress

Intravenous therapy was started, and during the next twenty-four hours the patient received 3 litres of a solution containing 0 18% sodium chloride, 4 3% dextrose, and 0 1% potassium chloride and 3 litres of 1 87% sodium lactate In addition he was able to take copious fluids by mouth and mist pot cit *B.P C* $^1/_2$ oz. four-hourly A rectal tube was inserted so that urine could be drained off continuously, and intramuscular streptomycin g 1 b d was given for the next five days in case of urinary infection

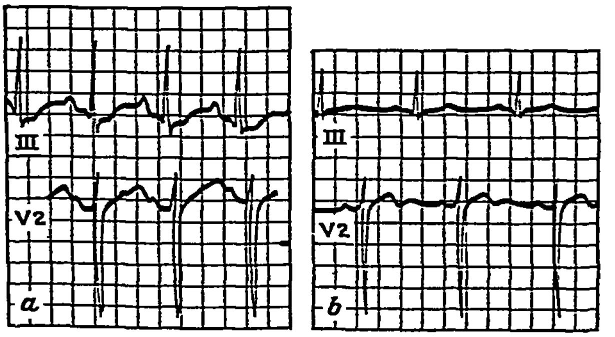
By the next morning the patient's condition was greatly improved He was obviously less dehydrated and could move his arms and legs, but he was still unable to raise his head from the pillow The blood chemistry showed improvement (see table, Oct 8) Intravenous therapy was stopped, but mist pot cit *B P C* and fluids were continued by mouth, salt being restricted The rectal drainage tube was removed after forty-eight hours He continued to improve symptomatically, and the plasma-potassium rose progressively to 4 5 mEq per litre on Oct. 10 (see table) The electrocardiogram had become normal (see figure, *b*)

The patient was discharged from hospital on Oct 14, 1958, feeling very well and taking a normal diet with no salt restriction He was given mist pot cit. *B.P C* $^1/_2$ oz b d and was advised to increase the dosage if any muscular weakness developed. He was instructed to pass urine at intervals of not more than three hours Since discharge he has attended as an outpatient He has remained well, playing football at weekends, and continues on potassium citrate regularly

The latest blood-chemistry findings (April 6, 1959) showed hyperchloræmic acidosis with raised blood-urea but normal potassium (see table)

Discussion

After ureterosigmoidostomy reabsorption of urea from the urine in the bowel results in a raised blood-urea which does not necessarily imply renal dysfunction Similarly, reabsorption of chloride ions by the colon preferentially to sodium ions accounts for the hyperchloræmic acidosis (Parsons et al 1952) Electrolyte disturbances are more severe when the ureters are transplanted into the cæcum



Electrocardiograms (leads III and V_2) *a*, Oct 7, 1958, showing sinus rhythm, PR interval 0 20 sec., QRS 0 12 sec., tall tilted P waves depressed ST segments, marked U waves which are taller than T waves in V_2 (plasma-potassium 1 5 mEq per litre) *b*, Oct. 9, 1958, normal appearance, with sinus rhythm, PR interval 0 18 sec., QRS 0 1 sec. (plasma-potassium 3 5 mEq per litre)

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or proximal colon than when they are transplanted into the sigmoid colon This has been demonstrated in animal experiments, in which the lower the level of the colon at which the ureteric transplant was inserted the lower was the mortality-rate (Boyce 1951) Similarly, in man there has been a higher mortality where the right ureter has been anastomosed to the cæcum and the left to the sigmoid colon (Kekwick et al 1951) These biochemical abnormalities may exist where renal function has been normal (Mitchell and Valk 1953)

Hypokalæmia, though less common than other electrolyte disturbances, may have more serious consequences Its precise causation is not fully understood, but it is thought to result partly from renal tubular dysfunction This may result from chronic pyelonephritis, which is almost invariably present in cases coming to necropsy (Graves and Buddington 1950) In addition, because of the excessive absorption of chloride, sodium, and urea from the bowel, there is obligatory osmotic diuresis resulting in loss of potassium (Stamey 1956) Apart from the renal factors, potassium may be lost into the colonic contents from the mucosa of the bowel (Parsons et al 1952, Stamey 1956) Potassium deficiency may cause weakness of voluntary muscles, progressing in extreme cases to flaccid quadriplegia, as in the present case

In cases of ureterosigmoidostomy, both doctors and patients should be aware of the possibility of serious electrolyte disturbances These are especially likely during an illness in which there is vomiting or diarrhœa, following excessive perspiration, or if constipation develops

As a prophylactic measure these patients should be instructed to evacuate the bowel of urine at intervals of three hours or less, they should ensure an adequate fluid intake, and it may be necessary to give regular supplements of alkali and potassium If they begin to feel weak or lethargic, electrolyte control will be required, and treatment should be aimed at correcting the metabolic abnormalities

Summary

Flaccid quadriplegia due to hypokalæmia developed in a patient nine years after ureterosigmoidostomy The patient presented with paralysis which was thought at first to be due to acute poliomyelitis, but which responded dramatically to correction of the metabolic abnormalities

Patients and doctors should be aware that preventable complications may follow this type of operation

We wish to thank Dr K O Rawlings for permission to publish this case and for helpful advice and criticism

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Addendum

Since this paper was completed, K G Lowe, J M Stowers, and W F Walker (*Scot med J* 1959, 4, 473) have described two cases of paralysis due to hypokalæmia —in one eleven years and in the other four years after ureterosigmoidostomy A W Steinbeck and J H Tyrer (*Brit J Urol* 1959, 31, 280) have reported the case of a man who had his first attack of paralysis twenty years after ureterosigmoidostomy and in the next five years had about a hundred similar episodes, since sodium citrate and potassium citrate have been given daily, there has been no further paralysis R A Straffon and A J Coppridge (*J Amer med Ass* 1959, 171, 139) have described two cases which presented with flaccid quadriplegia and with respiratory paralysis requiring treatment in a tank respirator Acute poliomyelitis and Landry's acute ascending paralysis had been provisionally diagnosed When investigations revealed severe hypokalæmia (ureterosigmoidostomy had been performed on both, six years and fourteen years before) treatment with potassium was started The response to treatment was dramatic, one patient being removed from the respirator within a matter of hours and the other by the next day

BROKEN TRACHEOTOMY TUBE AS A FOREIGN BODY

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Since tracheotomy became common in the treatment of respiratory poliomyelitis, and particularly since positive-pressure respiration was introduced,[1–3] many patients have had to wear tracheotomy tubes over long periods We describe here an accident to one such patient, arising from causes of which we were not at that time aware

The patient, a farmer's wife aged 35, was admitted to the department on Aug 17, 1958, with poliomyelitis During the first 24 hours severe paralysis of the trunk and extremities developed, and signs of bulbar involvement Tracheotomy was necessary, and the respiratory muscles remained paralysed Respiration was maintained by the Engstrom respirator, the Kifa cuirass respirator, and a rocking bed

On Feb 17, 1959, some respiratory infection was noticed There were signs of bronchitis, especially in the right lung, and a purulent discharge from the cannula When the cannula was changed, a large defect was found in it (*fig 1*), and an X-ray of

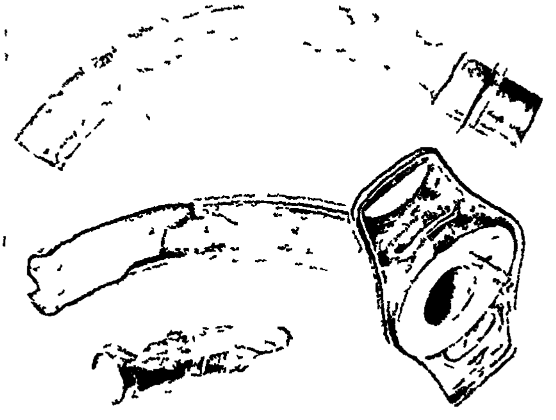

Fig 1—The broken tracheotomy tube

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[1] World Health Organisation Poliomyelitis Geneva, 1955
[2] Lassen, H C A Management of Life-Threatening Poliomyelitis Edinburgh, 1956
[3] Strøm, J Poliomyelitis Epidemic in Stockholm 1953 *Acta med scand* 1956, 154, suppl 316

he lungs showed a fragment in the right main bronchus (fig 2) ronchoscopy was performed and the foreign body was emoved The patient is still wearing a cannula and must be egarded as a chronic respiratory case

The cannula removed from this patient showed obvious racks on the outer surface, although the inner part looked intact We then examined all the cannulas in the department, and found 3 more which appeared faulty and on closer examination were seen to have cracks These cannulas were sent to the Oslo Material-Testing Station for investigation They were made of german silver, containing 18% nickel (the maker's statement) Magnification 40 times showed cracks in the alloy The split formation was caused by "season cracking" (splitting caused by long-continued high internal stresses in the surface and the action of a relatively weak corroding medium, usually one or other of the quaternary ammonium compounds) Fig 3 shows a photomicrograph ×360 of the numerous transcrystalline cracks

ig 2—X-ray of the lungs showing foreign body in the right main bronchus

The most remarkable thing about this damaged cannula was the widespread splitting, and it might have broken into several pieces The cracks could not be seen by the naked eye, but required a magnification of ×30 for their detection Straight transcrystalline splitting indicates "corrosion fatigue" in the metal this usually occurs when the metal is subjected to changing stresses, particularly in the presence of a corrosive This cannula was not subjected to mechanical stresses, and the split was probably caused by inner stress in the material from damage to the nickel coating In some cases (though not in ours) the bronchial secretion is alkaline

For many years, this department, besides using silver cannulas specially made to fit the respirator, has also used cannulas of german silver, because these are cheaper and can be thrown away as soon as they show signs of wear The routine for patients who have to stay long in a respirator is to change the cannula every 10–14 days In many parts of Norway the cannulas made of german silver are commonly called "silver cannulas" After this accident we shall in future use only pure silver cannulas, though these, being softer than german silver, will wear out sooner

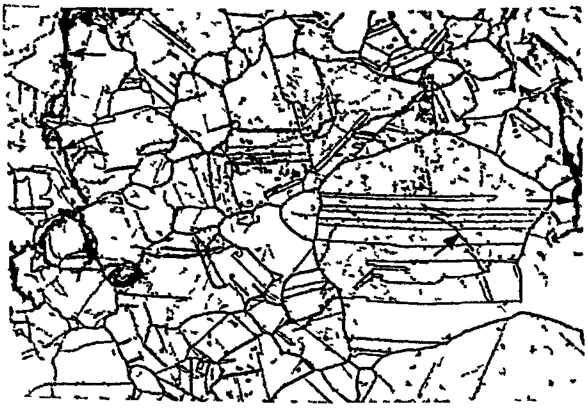

Fig 3—Photomicrograph of the cannula showing numerous transcrystalline cracks (×360)

Summary

Respiratory infection in a patient with poliomyelitis was found to be due to breakage of the tracheotomy cannula, part of which was found as a foreign body in the right main bronchus When put in place 14 days earlier it had appeared free from fault It was of german silver and the cause of the break was "season cracking" In chronic respiratory cases only pure silver cannulas should be used

Preliminary Communication

A NEW DIAGNOSTIC TEST IN AMYLOIDOSIS

SINCE it was introduced in 1923 by Bennhold,[1] the congo-red test has been widely used to establish the presence of amyloidosis However, no full agreement exists over the evaluation of the test Some workers consider that if more than 60% of the dye disappears from the blood within 45 minutes of intravenous injection, this may be taken as a sign of amyloidosis, but others [2,3] maintain that only a complete (99–100%) removal is conclusive

Side-effects are rare, but may occur In this department a patient who had an intravenous injection of congo red immediately showed a severe allergic reaction with dyspnœa, œdema of the face and larynx, and circulatory collapse He recovered

PRESENT INVESTIGATION

Patient A, with primary amyloidosis (confirmed by needle biopsy of the liver) and hypoalbuminæmia had ^{131}I-polyvinylpyrrolidone (^{131}I-P V P)[4] administered intravenously to rule out intestinal protein leakage caused by intestinal amyloidosis As part of the investigation he had Evans blue *U S P* intravenously at the same time 15 minutes later blood was withdrawn for determination of dye concentration[5] and radioactivity The initial distribution-volume of Evans blue is supposed to be identical with plasma-volume, and, whereas in all the other patients (about 60) examined until then, it had been lower than the distribution-volume of ^{131}I-P V P (usually by 15–50%), in this patient it was 10% higher

To confirm this finding, Evans blue and human serum-albumin, labelled with radioactive iodine, were injected simultaneously and the concentrations determined in plasma 15 and 45 minutes after the injection The 15-minute concentration was used to calculate plasma-volume Normally, the plasma-volume as determined with Evans blue (P V$_{E}$) or with ^{131}I-albumin (P V$_{A}$) are identical,[5–7] and the disappearance-rate does not differ within the first hour after injection, amounting to 6–12% per hour[8] However, in the patient with amyloidosis P V$_{E}$ (4600 ml) exceeded P V$_{A}$ (3150 ml) by 46% The disappearance-rate of Evans blue within the first hour was appreciably higher than that of ^{131}I-albumin as shown in fig 1

45 minutes after injection the ^{131}I-albumin concentration had decreased by 7%, and that of Evans blue by 30%, compared with the concentration 15 minutes after injection The

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[1] Bennhold, H *Dtsch Arch klin Med* 1923 144, 32
[2] von Preyss, J A *Medizinische*, 1957, 43, 1568
[3] Selikoff, I J *Amer J med Sci* 1947, 213, 719
[4] Gordon, R S *Lancet*, 1959, i, 325
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[8] Gregersen, M I *J Lab clin Med* 1944, 29, 1266

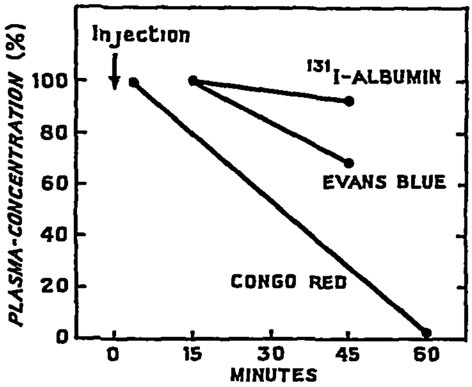

Fig 1—Disappearance-rate in blood of ^{131}I-albumin, Evans blue, and congo red in a patient with primary amyloidosis

The highest concentration measured is given an arbitrary value of 100

congo-red test was positive, 99% being removed from the blood in the interval 4 to 45 minutes after injection

With this new knowledge an old mystery was solved

9 months earlier a marked discrepancy between PV_E and PV_A had been found in patient B, extremely ill with ulcerative colitis and osteoarthritic spondylitis Investigation with ^{131}I-albumin had been undertaken, and to check that he remained in a steady state, PV_E was determined at 3-day intervals The anomalous results are recorded in the table (patient B)

First PV_E was nearly 3 times higher than PV_A subsequently PV_E decreased, suggesting that a certain saturation of the Evans blue binding-system had taken place

The patient had part of his colon resected, but died a few weeks later The only noteworthy macroscopical finding at necropsy was a big liver Microscopically, however, extensive amyloidosis was seen in the liver, spleen, and kidneys

PLASMA-VOLUMES AS DETERMINED BY ^{131}I-ALBUMIN AND EVANS BLUE IN 3 PATIENTS WITH AMYLOIDOSIS AND 1 WITH MYELOMATOSIS

Patient	Age and sex	Diagnosis	Date	Plasma-volume		Serum γ-globulin (g per 100 ml)
				Iodised albumin (ml)	Evans blue (ml)	
A	42 M	Primary amyloidosis	Jan 5	3150	4600	0 99
B	32 M	Ulcerative colitis, osteoarthritic spondylitis, secondary amyloidosis	April 13	3200		2 03
			„ 17		9430	
			„ 20		6710	
			„ 23		5910	
C	40 F	Myelomatosis, secondary amyloidosis	Feb 24	4670	14,400	0 97
D	73 M	Myelomatosis	Feb 20	3290	3260	8 09

A third patient (C) with myelomatosis and secondary amyloidosis, confirmed by liver biopsy, received simultaneous intravenous injections of Evans blue and ^{131}I-albumin. Blood samples were withdrawn after 4, 8, 15, and 45 minutes The results are shown in fig 2

The plasma concentration of Evans blue falls rapidly within the first 15 minutes and then more slowly, while the ^{131}I-albumin concentration shows a linear and slow decline like Evans blue in a normal person (top curve) The different disappearance-rate of Evans blue and ^{131}I-albumin is obvious 15 minutes after injection, when the dye concentration is 42% less than that of the 4-minute sample In this patient PV_E *(14,400 ml) exceeded* PV_A *(4670 ml.) by 208% (see table,* patient C) The congo red test was positive The patient cleared her blood completely of congo red within 60 minutes

DISCUSSION

This finding that Evans blue is removed from plasma much faster in amyloidosis than in any other state, and to such a degree that plasma-volume determined with Evans blue from a 15-minute sample may be more than 200% too high, has not been described before

Verel [9] in a series of 38 patients suffering from a variety of diseases found the ratio body/venous hæmatocrit as determined by Evans blue and ^{51}Cr-erythrocytes to be lowest (0 79) in a case of amyloidosis This may be a falsely low value due to an erroneously high PV_E

A diagnostic test could be based on these findings, and I would suggest one of the following two procedures

1 Blood samples are taken 4 (A) and 15 (B) minutes after the injection of a known amount of Evans blue If the dye-concentration of B is less than 80% of A, amyloidosis is probable

2 If equipment for radioactive measurements is at hand this test may be combined with a better one Known amounts of Evans blue and ^{131}I-albumin are injected immediately after each other (but not in the same syringe [10]) 15 minutes later blood is withdrawn, and distribution-volumes are determined If PV_E exceeds PV_A by more than 10%, the patient probably has amyloidosis

These tests may turn out to be more specific than the congo-red test, as the rapid removal of Evans blue can only be due to an abnormal non-circulating protein with a dye-binding power, which is many times that of the ordinary plasma globulins and perhaps nearly as high as that of albumin The abnormal protein could be in or close to the capillary wall Were it intravascular it would not affect determination of plasma-volume with Evans blue In a case of myelomatosis with a high concentration in the plasma of an abnormal gamma-globulin, the PV_E was correct (see table, patient D)

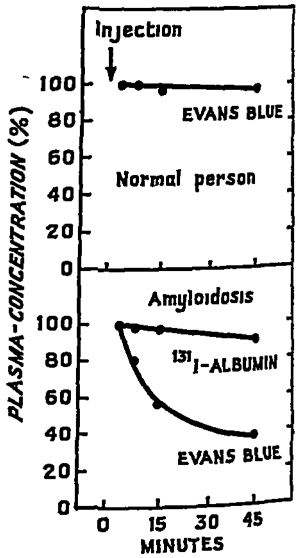

Fig 2—Plasma-concentration of Evans blue in a normal person and Evans blue + ^{131}I-albumin in a patient with amyloidosis

Concentration is given as a percentage of the concentration 4 minutes after injection

SUMMARY

The dye Evans blue, extensively used for plasma-volume determination, is removed at an abnormally high rate from the blood in patients suffering from amyloidosis Therefore it cannot be used for plasma-volume determinations in this disease On the other hand it can be of diagnostic value, and two new diagnostic tests using Evans blue are suggested for confirming the presence of amyloidosis

I wish to thank Prof H C Gram, Sundby Hospital, for kind permission to examine one of the patients with amyloidosis This work was supported by grants from King Christian X's Fund

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Medical Societies

ASSOCIATION OF CLINICAL PATHOLOGISTS

THE 64th general meeting of the Association was held in Cardiff, on April 7–9 We publish below a brief account of some of the contributions

Cross-infection in Hospital

Prof S D **ELEK** and Dr P C **FLEMING** (St George's Hospital) had made use of Gould's observation that in hospitals there was a detectable amount of penicillin floating in air, causing selective exclusion of penicillin-sensitive staphylococci from the noses of those in hospital They aimed to eliminate nasal carriage with a new experimental antibiotic (AB1241) which fulfilled the following requirements (1) it was active against all of 400 strains of *Staphylococcus pyogenes* tested, (2) it was active in concentrations of 1–5 µg per ml and highly bactericidal at about the bacteriostatic level, (3) resistance could not be induced in 12 strains by 20 serial passages through Szybalski gradient plates The substance was odourless and non-irritant A maternity unit was chosen for the spraying experiment because of the known high incidence of nasal carriage in infants Approximately 55% of daily nasal swabs taken from each of 58 newborn infants during their first ten days grew pyogenic staphylococci Daily spraying of 1 g of the drug was next carried out in one ward and nursery occupying about 15,000 c. ft using a commercial window-cleaning sprayer This halved the nasal carriage but failed to abolish it. Increasing the concentration to 1 g 4 times a day led to further reduction for the next 20 babies Thereafter a cumulative effect became manifest as the drug began to build up in the environment No pyogenic staphylococci at all were isolated from the next 24 babies during their ten days in hospital No resistant strains emerged, and no hypersensitivity phenomena were observed over the twenty weeks This seemed to be a simple and effective means of eliminating nasal carriage in babies and was put forward as a possible approach for the control of wound sepsis in hospitals

Dr **BERYL CORNER** and Dr W A **GILLESPIE** (Bristol) showed that the spread of staphylococcal infection in maternity hospitals was quite rapid once there was an accumulation of resistant strains The ordinary accepted methods of interrupting spread were disappointing in the long run The infection arose from adult carriers and was spread superficially by nose and skin, particularly the umbilicus By the continuous use of hexachloraphate powder and by the instillation of chlorhexidine ('Hibitane') and neomycin in the noses of mothers and babies there was a striking reduction in the staphylococcal rate in both mothers and babies—particularly in the follow-up clinics in the incidence of breast abscesses, and sticky eyes in the children It was evident, however, in the most recent survey that monilia were now taking a firmer hold in the wards, and in the last bacterial survey there were 25 cases of spots due to staphylococci, 3 streptococcal abscesses, and 72 cases of monilial infection

The Hospital Vacuum Cleaner

Dr J G **BATE** (Princess Louise Hospital) described how the bacterial content of the air from ten vacuum cleaners and three suction polishers in use in hospital wards was investigated Bacteria-carrying particles were counted by a slit-sampler operating inside a large polyethylene reservoir in which stationary samples of exhaust air were collected from a polyethylene wind-tunnel in which the cleaners were operated. Serial samples of 5 c ft were collected from machines before and after a thirty-minute continuous run during which the airflow was regularly interrupted every fifteen seconds in order to stress the filters With one exception the vacuum cleaners gave colony counts not exceeding 2 in 10 c. ft and retained not less than 97% of the number of airborne bacteria found in the room air immediately before the test. One machine consistently gave counts of up to 5 colonies, retaining only 90% of the aspirated organisms Suction polishers gave counts up to ten colonies, with retention between 90% and 94% The aerial disturbance caused by vacuum-cleaner exhausts was also investigated, slit-sampler counts following the discharge of exhaust inside a small room showed that with open jet exhausts *there* was an *immediate rise and fall in the number* of airborne bacteria, followed by a slow bacterial fallout over the next hour When the speed of the airstream was reduced by means of a diffusing device at the outlet, no sign of disturbance was detected

Vaginal Discharge

Dr J A **BOYCOTT** (Taunton) said that of 561 specimens of vaginal discharge from women between the ages of 15 and 50, 418 contained little or no pus The reaction, cytology, and flora of this non-purulent discharge made it probable that it was an exaggerated flow of the normal secretions of the vagina and cervix 134 out of 143 purulent discharges contained trichomonas, with a mixed and inconstant bacterial flora 9 purulent discharges appeared to be due to bacterial infection Candida were found in 1 purulent and 64 non-purulent discharges These yeasts might not be parasitic upon the vaginal epithelium but derive their nutrition from the secretions of the epithelium In children below 15 and in women over 50 the picture was different. The discharge in 14 out of 16 children and 16 out of 18 older women seemed to be due to bacterial infection

Aluminium and Pulmonary Fibrosis

Dr G B **MANNING** (Bolton) described the case of a man aged 22 who died in 1954 from pulmonary fibrosis 3 years 5 months before his death he had begun to work in an atmosphere heavily contaminated with aluminium powder The next man who took over the identical job died of pulmonary fibrosis in 1959, 4 years 9 months after starting this work. A third case of fibrosis of lung from the same works was first suspected from the X-ray appearances of the chest before the place of work was known This man had, in fact, spent only 1 year in that same factory [1] Further investigations showed that so far out of 20 men exposed to heavy concentrations of aluminium powder in the atmosphere for more than 6 months, 2 had died from pulmonary fibrosis, 4 had evidence of pulmonary fibrosis, and 11 had normal chests, and 3 had refused examination.

Anæmia in Pregnancy

Dr C **GILES** (Stoke-on-Trent) reported a controlled trial of prophylactic folic acid during the last trimester of pregnancy, 758 women who received oral folic acid and iron showed significantly higher hæmoglobin levels at term than 721 women treated with iron alone Megaloblastic anæmia developed in 20 cases of the control group but in none of the patients treated with folic acid This trial supported the concept that folic-acid depletion tended to occur in late pregnancy, even in the absence of megaloblasts in the marrow Analysis of 156 cases of megaloblastic pregnancy anæmia, diagnosed over a period of three years, suggested that an inadequate diet and intestinal malabsorption were important factors predisposing to megaloblastic anæmia Abnormally high fæcal fat excretion was found in 12 out of 41 cases investigated, but in none of 17 normal pregnant women When megaloblastic anæmias of pregnancy were classified according to the types and relative numbers of megaloblasts in the marrow an abnormal blood-group distribution, with a significant increase of group A, was found in cases with the more advanced degrees of megaloblastosis These findings suggested that folic-acid deficiency tended to occur in a large number of women in late pregnancy, but only in a certain group, with an inherited predisposition, would folic-acid depletion result in florid megaloblastic anæmia

Bone-marrow Grafting in Man

Dr J G **HUMBLE** (Westminster Hospital) said that in 6 out of 8 patients treated by whole-chest irradiation for malignant disease marrow function was restored to the sternum by stored autologous marrow In 4 out of 9 cases treated by massive chemotherapy marrow function was similarly restored The other patients died before marrow function could be restored Some evidence of effect of the treatment on the tumours was noted The danger of infection, especially moniliasis, was considerable Despite recent criticism, the results suggested that a true reseeding of the marrow spaces took place Using homologous transplants, 3 cases of aplastic anæmia and 5 of acute leukæmia had been treated No remissions had been obtained although the last leukæmic child treated was showing hæmatological recovery when overwhelming moniliasis supervened The use of stored autologous marrow gave a much greater margin of safety in the vigorous treatment of malignant disease

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[1] *Brit J industr Med* 1959, 16, 123

Intestinal Biopsy in Cœliac Disease

Dr A H CAMERON (Birmingham) described the histological findings in duodenal or jejunal biopsies from 37 children, of ages ranging from 3 months to 4 years Using a technique for estimating the relative surface area of the mucosa, the biopsies were separated into two groups The first showed no significant loss of mucosal surface area, and they came from 11 patients, 1 of whom had cœliac disease and had responded well to gluten-free diet the other 10 showed no clinical evidence of cœliac disease Of the remaining 26, the clinical diagnosis was cœliac disease in 21, probable cœliac disease in 4, and uncertain in 1 Only 1 was on gluten-free diet at the time of biopsy This group was subdivided according to the severity of the histological appearances The histological grading might be of value in evaluating response to therapy Dr Cameron concluded that biopsy was a safe and important method of investigation in steatorrhœa of childhood

Coagulation Tests on Capillary Blood

Dr KATHARINE DORMANDY and Dr R M HARDISTY (Great Ormond Street) reported a scheme for the routine investigation of coagulation disorders using free-flowing capillary blood 0 2 ml blood was taken into a buffered citrate-saline mixture and used for the "prothrombin and proconvertin" test of Owren and Aas [2] and the thromboplastin screening test of Hicks and Pitney [3], the clotting-time of the capillary blood [4] was also determined These three tests were used as screening procedures, accurate identification of any defects revealed could be achieved by assay procedures carried out on the same specimen of blood The sensitivity and accuracy of the tests were indicated by comparison with the results of tests performed on venous blood obtained simultaneously

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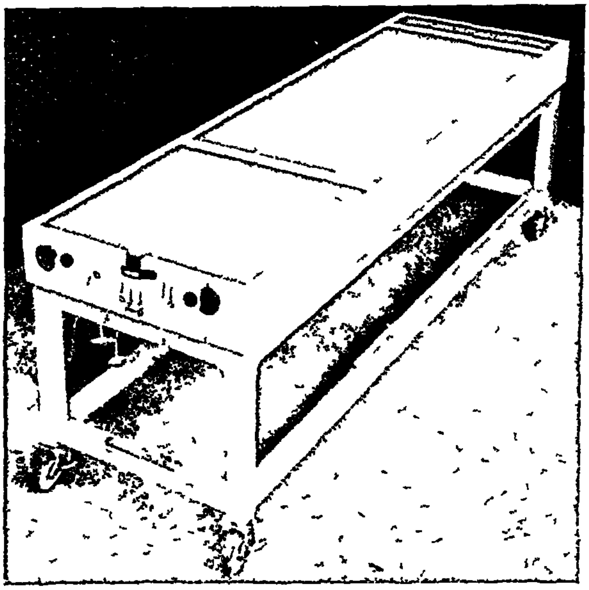
2 Owren, P A , Aas, K *Scand J clin Lab Invest* 1951, 3, 201
3 Hicks, N D , Pitney, W R *Brit J Hæmat* 1957, 3, 227
4 Dale, H H , Laidlaw, P P *J Path Bact* 1911, 16, 351

New Inventions

A TABLE FOR SERIAL ARTERIOGRAPHY OF THE ABDOMINAL AORTA AND LEG VESSELS

VARIOUS methods of serial radiography of the arterial systems of the abdomen and legs, using a single dye-injection technique, are available The special table here illustrated, which has proved satisfactory in the South Warwickshire group of hospitals, is a reproduction, with certain modifications in detail, of a table designed and pioneered by Prof J B Kinmonth, in association with the radiographic departments of St Thomas's and St Bartholomew's Hospitals

Three complete exposures of the abdomen and legs are obtained by using a series of sliding trays A device is incorporated to overcome the inevitable gap between abdominal and leg films if a conventional technique is used Casettes are employed for the abdominal pictures, and overlapping double-wrapped films for the upper and lower legs Two X-ray tubes are required, the lower covering both leg films This lower tube can be a standard hospital mobile X-ray Unit (60 mA) to which a special large rectangular cone must be fitted The pictures are improved by incorporating a wedge filter in this unit. Alternatively the different exposures required for the upper and lower leg can be obtained by using double-wrapped films of different speeds The table is loaded with films before the patient is placed there, and all further film changes are accomplished by one operator working at the head



By using an elevating device, or simply wooden blocks at the upper end, the table may also be used for full-length leg phlebography

I wish to thank Professor Kinmonth and Dr J W McLaren of St Thomas's Hospital for their assistance and kind permission to study their original plans, the staff of the X-ray department and the nurses at Warwick Hospital for their patient and willing help during the many clinical trials of the table, and the Cape Engineering Company of Warwick, who manufacture the table, for their interest, workmanship, and ability in overcoming the many technical difficulties encountered

Warwick Hospital,
Lakin Road, Warwick

C R SAVAGE
M.B Lond F R C.S.

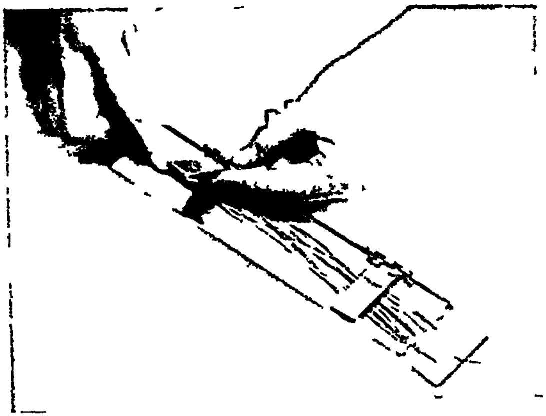
A DISPENSER FOR NYLON SUTURES

HOLDING suture material is not an important problem in general surgery, but for casualty work, where cheaper heat sterilised nylon sutures are often used, immediate access to a supply of previously sterilised sutures is desirable

A well-known means of dispensing sutures by threading them through a short rubber tube was used for a time in the casualty department of Leeds General Infirmary, but this proved inconvenient since the rubber deteriorated with use, and the sutures became untidy during boiling

A dispenser was therefore designed by Mr Maurice Ellis, consultant in charge of the department This was non-corrodible, held about twenty 14-in lengths of nylon firmly during sterilisation, and allowed any desired number of sutures to be removed easily when it was placed in a sterile instrument cupboard The dispenser comprised three stainless-steel helical springs held parallel in a rigid frame, the overall length corresponding to the length of the sutures Single strands of nylon could be pushed between the coils of the springs so that each was held firmly and could be withdrawn separately

But this device required several minutes to fill, and occupied a relatively large area in proportion to the number of sutures held I therefore designed a further device (see figure) Also made from stainless steel, it comprises a flanged base-plate 16 in long and 1–2 in wide with two flanged spring-loaded flaps, which hold an unsorted bundle of sutures Because the



sutures are thus clamped by four metal edges, a single suture may be withdrawn leaving the remainder undisturbed Each end of the base-plate slopes away for 1 in to facilitate picking up the sutures with instrument forceps This dispenser is easily and rapidly loaded, and is suitable for all gauges of nylon suture. It has been in use in the department for a year, and has proved reliable and convenient

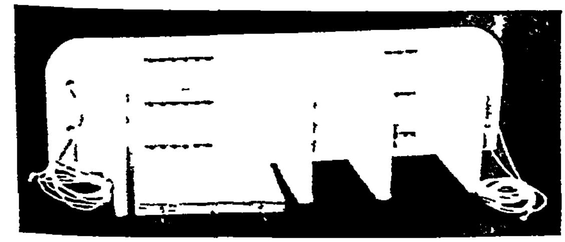
D BARNETT
B A Oxon
Casualty Dresser

University of Leeds,
Medical School, Leeds, 2

A FOOTBOARD TO KEEP THE FEET IN THE CORRECT POSITION

DEFORMITY of the feet is an end-result of many diseases Fixed plantar flexion not uncommonly follows footdrop, whatever its cause Sandbags are often the only means used to support the feet at right angle, but these rarely stay in place for long, and they tend to produce a claw-foot deformity

The simple footboard illustrated here consists of a wooden board 2 ft 6 in long and 9 in high, covered on its inner surface by thick orthopædic felt The central partition is fixed to the board, and is covered on both surfaces with felt The other four removable partitions are felt lined on their inner surfaces only They are fixed to the board by upper and lower screws and wing nuts, and by a central peg, passing through any set of the three parallel rows of holes



A foam-rubber pillow is placed under the patient's calves and the footboard is held firmly against the feet by cords which pass from the ends of the board and are tied at the bed head Two small rear supports (not shown in the photograph) prevent the board from tilting backwards The legs can be kept in adduction if placed between the central and inner removable partitions, or in abduction between the removable partitions External or internal rotation deformities at the hip, which may follow paralysis of the legs, can be slowly corrected by gradually moving the partitions nearer together If the knees are moderately flexed, a drawsheet, folded until it is 12–18 in wide, placed across the knees and firmly tucked under the mattress is often helpful. A bed cradle is unnecessary when the footboard is in place.

The footboard was originally made for me eight years ago by the hospital carpenter It is now manufactured by Messrs Charles F Thackray & Sons, of Leeds

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ÆSTHESIOMETERS

THE æsthesiometers described here have been designed for testing two different aspects of touch sensation

Threshold of Touch Feeling

The instrument shown in fig 1 consists of an engineer's sliding calliper suitably modified Two nylon threads of 0 02 in (0 5 mm) and 0 04 in (1 0 mm) diameter are passed through holes in the sliding part of the calliper and fixed by screws in the handle In testing a patient the tip of one of the threads is brought gently into contact with the skin and the thread is then distorted through a distance of two or three millimetres, this distance being judged by taking the tip of the other thread as a reference point The strength of the stimulus is directly related to the working length of the thread—that is, to the distance between the free end and the hole in the sliding part of the calliper The weight of the thread can be ignored provided the instrument is held in the same position relative to the skin surface when two areas of skin are compared

The threshold of touch feeling is greatly influenced by skin temperature so absolute values cannot be conveniently obtained Relative values, however, can be obtained by comparing an abnormal area of skin with a normal area Sensory maps can be easily made by using a stimulus which is just subthreshold in an abnormal area since this stimulus will probably be well above the threshold in neighbouring normal areas

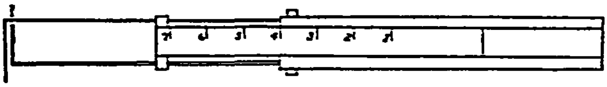

Fig 1—Æsthesiometer for touch feeling threshold (half actual size)

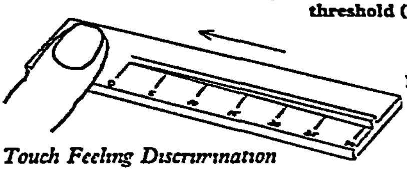

Fig 2—Æsthesiometer for touch feeling discrimination (half actual size)

Touch Feeling Discrimination

The instrument shown in fig 2 consists of a piece of transparent acrylic, 10 × 2 × 0 3 cm in size A ridge runs down the middle projecting 0 03 in (0 75 mm) at one end and gradually diminishing to zero about 2 cm from the other end The instrument is marked at points where the projection measures 5, 10, 15, 20, 25, and 30 thousandths of an inch, or in fractions of a millimetre if this is preferred. The markings are placed on the surface opposite to the ridge contrary to the appearance in the figure

The flat end of the instrument is pressed on the patient's fingertip and then moved lengthwise across the finger until the patient announces that he can feel the ridge This is done two or three times to allow the patient to improve his performance. The upper limit of normality is 0 01 in (0 25 mm) in all fingers except the fifth, in which the upper limit is 0 015 in Most subjects can feel 0 005 in on the index finger The test should be carefully restricted to the part of the phalanx midway between the centre of the whorl and the fingertip, for proximally the threshold rises rapidly Care has also to be taken to keep the ridge moving in the direction of its long axis, for a movement in any other direction causes the ridge to scrape the skin, producing something akin to a vibration feeling This test is not influenced by skin temperatures

This test can be substituted for tests of postural sense in the hands and for tests of two-point discrimination, graphæsthesia, and so on It is a more sensitive test and is easier for the patient and the examiner

Touch feeling discrimination and other relevant matters are discussed elsewhere [1]

Both instruments can be made without difficulty on a $3^1/_2$ in lathe with a milling attachment Information on making the instruments can be obtained from me

STEWART RENFREW
M.B , B.SC. Glasg , M.R.C.P

Royal Infirmary,
Glasgow

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[1] Renfrew, S , Melville, I D *Brain* (in the press)

Reviews of Books

Reflections of a Medical Investigator

R A McCance, c.b.e , f r c p , f r s , professor of experimental medicine, University of Cambridge. London Pitman Medical Publishing Co 1959 Pp 63 7*s* 6*d*

This book contains four lectures delivered recently in Holland, and the reader will be rewarded by an insight into the opinions of a distinguished medical investigator The opening chapter deals with some of the problems of modern medicine in which the applications of high-powered technology have to some extent been counterbalanced by equal concentration on the psychological aspects of illness The great complexity of the doctor's responsibility for the patient's soma as well as his psyche is discussed with sympathetic insight. In the succeeding lectures Professor McCance covers many topics which he has made his own Success in prolonging life brings us to the issue of food-supply versus population growth. It is to this very theme that Professor McCance has devoted much of his working life He has dealt with famine and undernutrition at one extreme, and at the other he reveals his interest in over-nutrition and obesity He also discusses the unique and temporary physiological states of early infancy where poor temperature regulation is counterbalanced by tolerance of oxygen lack The problems of water balance at this early period of life, before the kidney has developed its full adult physiological functions, make fascinating reading The author is at his best when he is dealing with his own investigations He is perhaps a little less critical when discussing such questions as the relationship of dietary fat to atheroma. It is tempting to accept the simple explanation that the level of blood-cholesterol is all-important, but to do so ignores a vast accumulation of knowledge implicating a great variety of other factors This little book will repay the few hours required for its study by its stimulating thoughts which are not readily available elsewhere

Respiratory Physiology and its Clinical Application

John H Knowles, m.d , chief of the pulmonary disease unit and assistant in medicine, Massachusetts General Hospital, instructor in medicine, Harvard Medical School Cambridge, Mass Harvard University Press London Oxford University Press 1959 Pp 256 42*s*

The first part of this book describes different aspects of pulmonary function in health and disease, gives an account of tests in current use, and discusses the interpretation of findings Emphasis is placed on tests which demand only those laboratory facilities likely to be available to the practising physician The second part of the book describes the alterations in pulmonary function associated with individual disease processes The story is told as far as possible in words, statements in symbols and equations are translated for the benefit of readers unfamiliar with the language of mathematics The content of this work is first-class, the presentation succinct, and the style lucid There is an excellent bibliography The author has aimed at the interested clinician and it is safe to predict a palpable hit

Christ and Freud

Arthur Guirdham, d m , b sc , d p m London Allen & Unwin 1959 Pp 193 21*s*

The author gives his personal views on the relationship between psychiatry and religion, comparing and strongly criticising doctrinaire aspects of both religion and psychoanalysis The Church's preoccupation with sexual sin and guilt and the analytic overemphasis on the avoidance of frustration he views with disapproval, although religious experience, distinguished from "Religion", and many Freudian ideas are regarded with sympathy On the practice of psychiatry he says much and attacks the tendency to become preoccupied with the patient's possibilities of self-expression, personality development, and social participation He favours instead the negation of personality by techniques of contemplation, self-analysis, and relaxation, showing throughout the book that sympathy for Buddhist concepts which appears to be the contemporary trend The book is interestingly written and not without humour, though it is marred by trenchant criticism of ideas no longer held and a few doubtful assertions —for example, that neuroses are of infinitely smaller incidence against a Buddhist or Hindu background

Laboratory Manual of Pediatric Micro-Biochemical Technics

Editors Donough O'Brien, m d , m r c p , Frank Ibbott, f i m l t , department of pediatrics, University of Colorado Colorado University Medical Press London H K Lewis 1959 Pp 164 21*s*

This spiral-backed manual, printed in typescript form, has been prepared at Colorado University by the two authors, who had previously been associated with The Hospital for Sick Children, Great Ormond Street The manual is intended for residents in clinical pathology passing through the chemical pathology departments in the course of their more general training, and also for trainee technicians and other clinical chemists who have need of techniques specially adapted for children Methods are alphabetically arranged, rather as they would be in a laboratory notebook, providing a useful form of ready reference

Yours by Choice

A Guide for Adoptive Parents Jane Rowe London Mills & Boon 1959 Pp 148 15*s*

The title rather suggests that those who would like to choose a child for themselves can do so, and the subtitle that the contents will tell them how to set about it Actually the reader will learn that choice is severely limited and that many who think of adopting should search their hearts and refrain The rather complex legal machinery, varying from country to country even within these islands, is only lightly sketched, there is no index, and as a guide it must be called incomplete. As a book of advice, especially on the many emotional problems inherent in adoption and arising from it, on the influences of inheritance and environment, and on the credits and debits of the undertaking, it is well informed, well balanced, and a useful addition to the growing literature of the subject Adopters, prospective or actual, will find it interesting and thought-provoking and are almost certain to get help from its pages, but they should regard it as a commentary rather than a guide

Oxygen Supply to the Human Fœtus (Oxford Blackwell Scientific Publications 1959 Pp 313 47*s* 6*d*)—There were twenty-one distinguished participants in this symposium organised jointly by the Council for International Organisations of Medical Sciences and the Josiah Macy, Jr , Foundation, and held in December, 1957 This book is a well-produced record of their deliberations, ably edited by Prof James Walker and Dr A C Turnbull It is not a verbatim report and there is possibly some loss in spontaneity and speculation, although revision and rearrangement have made it coherent and readable Three main areas are fully explored the physiology of oxygen transport in fœtal blood, a subject about which much is known, although the practical importance is undetermined, the uteroplacental circulation, a problem of immense significance about which almost nothing is known, though the contributions of Ramsey, Metcalfe, and Browne are all exciting pioneer ventures, and, thirdly, the measurement of cord-blood oxygen levels, a controversial subject which is fully discussed with differences and difficulties frankly reported Throughout runs the troubling thought that, however meticulously sampled and analysed, the cord-blood at birth may not be wholly representative of "the oxygen supply of the human fœtus" Anyone interested in the fœtus and infant would profit by reading this very useful book for one thing readers will be led away from the pitfall of too facile a translation of experimental results to clinical practice, and they will appreciate the slow and painful way in which fundamental knowledge in this area is being acquired

THE LANCET

LONDON 7 MAY 1960

Renal Hypertension

THE growing recognition that unilateral renal disease of many different kinds can cause high blood-pressure confronts the clinician with a particularly difficult dilemma For on the one hand it encourages him to hope that he may meet the occasional case of hypertension which will respond dramatically to surgery, while on the other it faces him with problems of diagnosis and treatment which seem to grow daily in complexity

In the first place curable renal hypertension is much less common than, and at the same time clinically indistinguishable from, essential hypertension Secondly, some of the methods used in its detection, such as aortography, are technically difficult, by no means free from danger,[1] and not always reliable The first problem, then, is to choose which patients should be submitted to special investigation, and a considerable number of pointers have been suggested[2–4] since PLATT[5] first pointed out that lack of a family history of hypertension may sometimes be significant Thus PEART,[2] whose Goulstonian lectures for 1959 include a valuable analysis of the problem, mentions an abrupt transition from the benign to the malignant phase, polyuria and proteinuria, disparity in size of the kidneys, and, in the case of stenosis of a renal artery, loin pain, leucocytosis, and a murmur over the abdomen Unilateral impairment of renal function is also suggestive To these CONNOR et al[3] would add the onset of hypertension at an unusually early or late age—that is, under 30 or over 50—and a history of abdominal injury None of these pointers can ever be more than suggestive. The renal disease may be only apparently one-sided If it is in fact unilateral it is not necessarily the cause of the hypertension And if it is the cause it may have led to secondary hypertensive damage in the opposite kidney[6] What is clearly needed is a reliable criterion for resolving these complexities Some recent work by HOWARD et al[3 7] at the Johns Hopkins Hospital goes at least part of the way towards providing such a criterion

The work was prompted by the observation in animals[8 9] that in hypertension caused by constricting one renal artery the urine excreted by the "ischæmic" kidney is greatly reduced in volume and contains an abnormally low concentration of sodium In a series of 210 hypertensive patients the Baltimore workers passed catheters up both ureters and compared the volume and sodium content of the urine from the two kidneys In 18 of these patients a kidney was later removed in the belief that it was causing the hypertension In 8 out of 9 patients whose hypertension was not relieved by nephrectomy the volume of the urine from the affected kidney was reduced, often considerably, but the sodium concentration was either equal to or *greater* than that of urine from the opposite kidney On the other hand, in 9 patients relieved or cured by nephrectomy both the volume and the sodium concentration of urine from the affected kidney were reduced—the volume by at least 50% and the sodium concentration by 15% or more These results suggest strongly that this test should be applied to all hypertensive patients before renal surgery is undertaken But, as the Baltimore and other workers point out,[3 4] failure to demonstrate unilateral impairment of renal concentration of sodium does not necessarily imply that the kidney concerned is not causing hypertension One situation where such a negative result may be misleading is where the underlying circulatory abnormality—whether it be pyelonephritis,[10] stenosis of a major artery, or any other lesion—may involve only a portion on one kidney, the rest of which may follow the excretory pattern of the opposite kidney

The clinician's problems do not end with the decision that a kidney is probably at fault, for he has yet to decide on treatment. In some cases nephrectomy is the only choice, but in others, and especially in renal arterial stenosis, a wide range of more difficult operative measures have to be weighed against simple nephrectomy[2 3] Many clinicians have been disappointed with the results of operation But where thorough investigation and careful selection of patients have been possible, the proportion of favourable results has been around 50%[3 4 11] This is very good in the circumstances, but it is still not good enough It must be remembered that erroneous selection for operation will not only do no good it may aggravate the hypertension, for in experimental hypertension removal of normal kidney tissue raises the blood-pressure considerably[6]

All in all there can be few more difficult problems in practical medicine today, but great progress has been made, and to cure even the occasional patient of severe hypertension is no small achievement

Only Isoniazid

IN severe pulmonary tuberculosis isoniazid alone gives results inferior to those obtained with streptomycin and isoniazid, streptomycin and *p*-aminosalicylic acid (P.A.S.), or isoniazid and P.A.S. The two regimens most suitable for large-scale use are isoniazid with P.A.S., and isoniazid alone Both these drugs are given by mouth, so large numbers of patients can be treated with a relatively small nursing staff, but P.A.S. has the disadvantages of high cost, large bulk, and gastrointestinal upset Isoniazid alone is, therefore, a more attractive treatment The use of isoniazid alone should be neither advocated nor condemned from its effects on a single type of the disease in the past such generalisations have impeded progress in the chemotherapy of tuberculosis The three main questions to be investigated are (1) the efficacy of isoniazid alone in treating patients with cavities and tubercle bacilli in the sputum, (2) the efficacy of isoniazid alone, once the sputum has been made negative by combined drug therapy, and (3) the efficacy of isoniazid alone in treating from the start patients with no cavities and a negative sputum (this group would include those whose only abnormality is a positive tuberculin skin test) Even these divisions may be too general Results obtained in hospital or by a well-staffed and efficient clinic might differ considerably from those in less favourable circumstances Moreover, in certain circumstances the results in a particular class of patients might be much superior with PAS and isoniazid together, whereas in other circumstances the difference might be less because more of those in the isoniazid group took the drug as prescribed than did those in the isoniazid-PAS group It is, of course, impossible to carry out controlled trials in all the possible combinations of circumstances that are found in practice throughout the world, and some extrapolation is necessary; but this must be applied cautiously

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[1] *Lancet* 1958 i 1058

[2] Peart, W S *Brit med J* 1959 ii, 1353

[3] Connor T B, Thomas, W C, Haddock, L., Howard, J E *Ann intern Med* 1960, 52, 544

[4] Page, I H., Dustan H P, Pontasse, E F *ibid* 1959, 51 196

[5] Platt, R *Quart J Med* 1948 17, 83

[6] Wilson, C, Byrom, F B *ibid* 1941, 10, 65

[7] Howard J E, Berthrong, M., Gould, D M, Yendt, E R *Bull Johns Hopk Hosp* 1954, 94, 51

[8] Mueller, B B, Surtshin, A, Carlin, M A, White, H L *Amer J Physiol* 1951, 165, 411

[9] Berliner, R W, Davidson, D G *J clin Invest* 1957, 36, 1416

[10] Kincaid-Smith P *Lancet*, 1955, ii, 1263

[11] Yates-Bell, J G *Brit med J* 1959, ii, 1371

The Medical Research Council's Tuberculosis Research Unit has carried out an impressive series of controlled field studies in the past fourteen years, each trial having been designed to answer one or more specific questions In a joint trial[1] the results of twelve months' treatment of East African patients in hospital with isoniazid in high and low dosage, and with a low dosage of isoniazid given with PAS, have been compared

The patients all had acute bilateral pulmonary tuberculosis with tubercle bacilli in the sputum, the cultures before treatment being sensitive to both drugs One group (40 patients) received 100 mg isoniazid twice daily A second group (37 patients) received about 20 mg isoniazid per kg body-weight in two equal doses, those under 100 lb (45 4 kg) receiving 800 mg daily, those above 100 lb and below 120 lb (54 3 kg) 1000 mg, and those 120 lb or more 1200 mg, this high-dose group also received 200–300 mg pyridoxine (about 5 mg per kg body-weight) each day A third group (35 patients) received 100 mg isoniazid and 5 g of the sodium salt of PAS twice daily in cachets containing both drugs together Both clinically and radiographically the group treated with isoniazid and PAS fared the best, the high-dose isoniazid group came next, and the low-dose isoniazid group did the least well The bacteriological results are more important, for from these may be estimated the speed and extent of the decline of infectiousness in the groups and the emergence of resistant strains of bacilli After three months' treatment 88% of the isoniazid/PAS group had a negative smear, compared with 69% of the high-dose isoniazid group and 54% of the low-dose isoniazid group After twelve months the culture results on single specimens were negative in 84% of the isoniazid/PAS group and in 67% and 57% of the high-dose and low-dose isoniazid groups respectively Because 5 in the low-dose and 6 in the high-dose isoniazid group had had chemotherapy changed because of deterioration, the twelve-month results give an unduly favourable picture To allow for this and to give a more comprehensive assessment of the bacteriological status, the classification used by the Tuberculosis Chemotherapy Centre in Madras[2] was employed, the patients whose treatment was changed being classed as "bacteriologically active" By the stringent definition of all available cultures in the tenth, eleventh, and twelfth months being negative on culture, 58% of the isoniazid/PAS group were "bacteriologically quiescent" after twelve months, compared with 34% and 25% in the two isoniazid groups The proportions "active" were 19%, 54%, and 61% respectively Sensitivity tests of cultures after six months' treatment showed isoniazid-resistant strains in 4 (13%) of the isoniazid/PAS group, 16 (47%) of the high-dose isoniazid group, and 22 (61%) of the low-dose isoniazid group The corresponding proportions at twelve months were 19%, 33%, and 53% The catalase activity of these strains is unfortunately not stated

This study shows clearly that in patients with severe infectious pulmonary tuberculosis treated in hospital isoniazid 100 mg twice daily is much less effective than the same dosage of isoniazid with 5 g sodium PAS twice daily Increasing the dose of isoniazid to about 20 mg per kg body-weight, given with 5 mg pyridoxine per kg body-weight, improves the results but does not bring them up to those obtained by combined treatment There is some evidence that pyridoxine may interfere with the action of isoniazid,[3] [4] so in this trial the effective dose of isoniazid may have been less than the dose ingested Better results might have been obtained without pyridoxine, but with more toxic effects on the central nervous system Pyridoxine is expensive, at hospital prices in Great Britain isoniazid and pyridoxine in the doses used in the MRC trial would cost from *2s 6d* to *3s 6d* a week for each patient, compared with *3s* for isoniazid with PAS The weekly cost of 200 mg isoniazid daily would be 2½*d* per patient But in mass treatment without adequate radiographic and bacteriological facilities, low doses of isoniazid alone seem unsuitable for infectious patients, and with high doses of isoniazid, although the bacteriological results are better, either pyridoxine must be added, bringing the cost to approximately that of isoniazid and PAS, or else a high incidence of peripheral neuritis must be accepted

Little is known about the efficacy of isoniazid alone, once the sputum has become negative on culture Possibly the bacterial population has by this time become small enough to be contained or killed by the continued isoniazid, the small isoniazid-resistant fraction being dealt with by the body's defences alone But there seem to have been no satisfactory trials of such treatment, and without their support few clinicians would willingly change their practice of continuing two drugs for eighteen months to two years—though it may be unnecessary to continue the same doses of the drugs or to give them as frequently as in the early stages Investigation of regimens for continued treatment would be difficult, but the results might lead to considerable saving of money and enable better initial treatment to be given to larger numbers

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[1] East African/British Medical Research Council Isoniazid Investigation *Tubercle, Lond* 1960, 41, 83

[2] Tuberculosis Chemotherapy Centre *Bull Wld Hlth Org* 1959, 21, 51

[3] McCune, R, Deuschle, K., McDermott, W *Amer Rev Tuberc* 1957, 76, 1100

[4] Boone, I W, Strang, V G, Rogers, B S *ibid* p 568

Isoniazid has been used extensively for treating people whose only evidence of tuberculosis is a positive tuberculin skin test.[5] [6] Unfortunately, there is no information yet about the risk of isoniazid-resistant strains of tubercle bacilli emerging if the patient becomes infectious later It seems to be agreed that this risk is probably very small, but in planning mass treatment of non-infectious patients, even an approximate estimate of its extent would be helpful Too little is known also about the long-term effects of any type of chemotherapy of patients with radiographically manifest lesions but no evidence of infectiousness or progression The Tuberculosis Society of Scotland [7] carried out a controlled study, using isoniazid and P A S, in patients with pulmonary lesions of " doubtful " activity and over a period of two years found fewer relapses in the treated group In a study by HALL et al [8] of 27 patients in whom there had been no radiographic change for at least three years and who had not previously received chemotherapy, there was no deterioration during a year's prescribed treatment, of 28 who were observed but not treated 1 deteriorated The patients received isoniazid with calcium benzoyl P A S, and as this substance gives such low concentrations of P A S in the serum [9] the effect of the combination might be regarded as almost the same as that of isoniazid alone PHILLIPS [10] reported that in patients with slight or moderately advanced disease without cavities the results with isoniazid alone were probably equally as good as those with isoniazid and P A S The M R C East African study has provided a little further information There were 25 patients with no or only slight cavitation at twelve months the numbers with single sputum specimens negative on culture were 8 out of 10 in the isoniazid/P A S group, 3 out of 3 in the high-dose isoniazid group, and 7 out of 11 in the low-dose isoniazid group

Isioniazid alone is now being advocated as part of the programme to eliminate tuberculosis in the U S A A conference arranged by the U S Public Health Service and the National Tuberculosis Association has recommended [11] that chemotherapy be applied primarily as a " public health tuberculosis control measure ", and that all resources be mobilised " for a widespread application of the scientifically demonstrated and medically accepted procedures of adequate chemotherapy " The conference did not specify the forms of chemotherapy OATWAY [12] had previously suggested giving isoniazid alone for at least a year to those believed to have " inactive " tuberculosis, and ISRAEL [13] advocates a vigorous campaign to treat with isoniazid those with " inactive " lesions or with lesions " of doubtful clinical significance " McDERMOTT,[14] however, commenting on the recommendations of the conference, suggests that the safety of extending the use of isoniazid alone beyond those with positive tuberculin reactions but without obvious disease is " a matter of serious debate " ISRAEL contends that such extension would bring the anti-tuberculosis campaign in the U S A to a dramatic end, and that, if a campaign of elimination has to be deferred for many years until evidence of the effectiveness of isoniazid alone is obtained, " anti-tuberculosis programs will fizzle out and the opportunity for a telling blow will have been lost " The arguments for an isoniazed attack on tuberculosis throughout the world command respect, but it is doubtful whether such an immense enterprise should be initiated without some valid evidence that the cost and trouble are worth while

Annotations

PSYCHIATRY AND THE MEDICAL STUDENTS

IT is often (and rightly) said that British medical schools pay too little attention to the undergraduate teaching of psychiatry, but few who heard Prof John Romano on April 27 can before have realised just how great the gulf is between curricula on either side of the Atlantic Speaking at the London Hospital Medical College, Dr Romano placed a heavy task on teachers of psychiatry—essentially this was the " scientific humanisation of biology " They must teach the sequence of events in human growth and decline, and the relations between the patient and others, especially the physician, and in turn the physician's relations with ancillary staff The student needs to learn the history of the concepts of health and disease leading to the current multiple-cause " open " system, and how to listen to and record the patient's story He must become aware of changes in medicine and in society, and be sensitive in perceiving certain types of criminal and social behaviour as variants of health and sickness He needs to grasp the uniqueness of the individual human being and appreciate the normal emotional crises of family life, but above all the teacher must foster the critical pursuit of knowledge and prepare the student to handle patients who manifest pain, anger, fear, anxiety, shame, and guilt in various psychological and somatic ways It was essential, continued Dr Romano, that we put behind us the vague dichotomy of " scientific " bodily disorder versus " intuitive " psychiatry, a logical approach to the mind is increasingly possible and the useful collaboration of psychoanalytic institutes with medical teaching in the U S A. helps in presenting the student with a framework of hypotheses The Americans, one might add, have an advantage over us in this, for most of our teachers of psychiatry are so incapable of making up their minds on Freud that they ignore his massive contribution Despite the distressing susceptibility of American psychiatry to psychotherapeutic and pharmacological fads, Dr Romano thinks that it holds a satisfactory position between Russian environmentalism and European determinism High standards of life, ease of communication, and freedom from catastrophic disease had allowed the discipline to advance more readily, perhaps, than elsewhere The vigour of American psychiatry was certainly suggested by the extensive undergraduate preparation which tried to accomplish the triple aims of training appropriate to future psychiatrists, family doctors, and other specialists.

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[5] International Tuberculosis Conference *Bull Un int Tuberc* 1959, 29, 152

[6] Lambert, H P *Amer Rev resp Dis* 1959, 80, 648

[7] Tuberculosis Society of Scotland *Tubercle, Lond* 1958, 39, 129

[8] Hall, Z M, Zorab, P A, Jefferson, K E *ibid* 1960, 41, 47

[9] Leading article *ibid* 1959, 40, 133

[10] Phillips, S *Amer Rev resp Dis* 1959, 80, 641

[11] Recommendations of the Arden House Conference on Tuberculosis *ibid*, 1960 81, 482

[12] Oatway, W H *ibid* 1959, 80, 108

[13] Israel, H L *ibid* 1960, 81, 581

[14] McDermott, W *ibid* p 579

Subjects covered in the two preclinical years at Rochester, New York, are personality growth, psychopathology, interviewing, and the patient-physician relationship. 70 students attend two-hour weekly sessions over the first year of thirty-six weeks, for a lecture followed by discussion in small groups, each under a senior staff member. In the second year the students spend two $1^{1}/_{2}$-hour sessions per week and there is attendance at nurseries and a course in history-taking. Films, tape-recordings, and one-way screens (with the patient's knowledge) are freely used and the course is compulsory. It is rightly held that such study is basic and fundamental to the whole of medicine. In the third year, students work in the 775-bed hospital in which 86 beds are devoted to adult and 12 to child psychiatry, and in the outpatient department, where 12,000 patient-visits were made in 1959. 6 to 8 students at a time spend four weeks full-time serving 2–3 inpatients each per week. There are no clinical lectures, but seminars are held and the very large psychiatric staff (18 full-time, 34 part-time plus 24 residents and research fellows and 6 interns) allow for continual individual teaching and supervision. The fourth-year course is much the same, with outpatient responsibility and supervised individual psychotherapy with patients and their families. Liaison with medical and pædiatric departments is close, and visits are made to the Rochester State Mental Hospital (3500 beds) and to institutions for epileptics, delinquents, and defectives. Students with aptitude and interest may extend their course and undertake research, or join colleagues from other universities for special elective work during the summer. The teaching process itself is constantly under examination and review by students and teachers alike. The fuller approach may be easier for American students who, at 21–22, come to their studies at a maturer stage, but the course is emphatically pedagogic rather than therapeutic. Although, as Dr Romano admits, American developments in this field are rather uneven, he hopes that his faculty is developing that systematic approach to man's mind, his emotions and relationships with others which, with help from the physical sciences, must lead to a basic science of human behaviour.

Compared with the somewhat puny British efforts, this exhaustive training has an almost unreal grandeur and is unlikely to have other than a paralysing effect on deans of medical schools. In their recent valuable survey of psychiatric teaching here, the British Medical Students' Association have recorded an average of thirty-one hours' total lecturing over 17 medical schools, with about 3 ward-rounds and 8 outpatient sessions, nor is it likely that those schools failing to reply were any better.[1] Provision was alarmingly disparate, and the students showed themselves to be well in advance of their mentors in demanding more teaching, particularly in clinical work and psychotherapy.

A NURSE'S WORK

IN the U.S.S.R. psychoneurosis is one of the diseases for which nurses may receive industrial injury compensation, in Uruguay nurses receive a pension equal to their full salary at the age of 60, the United Kingdom is one of the countries in which the hourly rate of pay of a hospital staff nurse is lower than that of an unskilled labourer —there are three thought-provoking findings in the International Labour Office's study of the nursing profession.[2] Administrators, matrons, doctors, and members of hospitals boards and committees will find it informative and stimulating reading.

With the expansion of health and welfare services more and more nurses are working in clinics, factories, and the patients' homes, but the majority are still hospital-bound, and the conditions of work in hospital are inevitably criteria for the whole profession. The chief reason for the continuing wastage of nurses is marriage, yet, as the report points out, the arrangement of working hours in hospitals is not consistent with family life. Hospitals are trying to maintain a continuous service throughout the twenty-four hours of the day and the seven days of the week. Greater flexibility in the organisation of hospital work, it is suggested, would help to attract married nurses. One possible modification of the traditional pattern of hospital care is Monday-to-Friday wards.[3] Another possibility, as so many girls are marrying in their teens, would be to recruit more male nurses. At present the percentage of men in the profession varies: Austria has 1%, Barbados 0%, the United Kingdom 5%, Trinidad and Tobago 22%.

A chapter on health protection draws attention to the risks, old and new, to which nurses are exposed in their work. Shift work, which switches periods for sleep and work, makes special demands on nurses' health, and this is apt to be overlooked by hospital administrators who work regular "office hours". In most countries night duty is longer than day duty, but in Israel night duty is restricted to thirty-six hours a week while the day-duty week is forty-seven. The I.L.O. experts recommend "that occupational diseases and injuries connected with nursing work should be studied on a continuing basis and redefined at periodic intervals for purposes of entitlement to social security benefit." Nurses who have had to change their profession because of a violent allergy to one of the new pharmaceutical products, and others who have contracted an infection from a penicillin-resistant staphylococcus, will hope that this will lead to speedy official recognition of contemporary nursing risks.

RECURRENT RHEUMATIC FEVER

INHERENT in every attack of rheumatic fever is the threat of another. How reliably does the pattern of a first attack enable the severity of a recurrence to be predicted? The answer to this question, always important to an anxious parent, has assumed greater significance since the introduction of effective means of reducing the risk of recurrent attacks.[4] After observing a large number of children and young adolescents who had had at least two attacks, Feinstein and Spagnuolo[5] have found that recurrences run very true to the form of the first attack, particularly as regards cardiac features.

Their investigation at first embraced 24 patients who had been examined in one institution and to whom uniform criteria for the diagnosis both of rheumatic fever[6–8] and of valvular disease had been applied. In this group both initial and subsequent attacks were personally observed by the authors. To these cases were later added 137 more, personally examined under the same uniform conditions only in recurrent attacks; data concerning the first attack in this second group were derived from the records of other physicians.

The results of this investigation were strikingly clear-out. With very few exceptions patients who had no organic murmur during one attack emerged equally unscathed from the next If an organic murmur had been audible during the earlier illness cardiac damage persisted, recurred, or increased during subsequent episodes 61 patients escaped damage to valves in 129 attacks of rheumatic fever, and in 90 such damage was evident in each of their 211 attacks This left only 10 cases in which organic murmurs were recorded for the first time during a recurrence, all were cases in which information about preceding attacks was extracted from the records of other physicians, and in 8 the negative auscultatory findings in these past episodes were regarded as questionable Most of the patients were between 6 and 11 years of age, and within these limits cardiac damage had no predilection for any age-group As Feinstein and Spagnuolo point out, this observation in a restricted age range does not invalidate the accepted concept that older patients with a first attack of rheumatic fever are less liable to cardiac complications In patients who escaped damage to their hearts the pattern of non-cardiac manifestations—arthropathy, choras, abdominal pain, erythema marginatum—in one attack tended to repeat itself in later attacks, but this tendency was less distinct when heart lesions were present

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[1] Report on the Teaching of Psychiatry and Psychological Medicine in British Medical Schools. British Medical Students' Association. (Undated, I am pretty sure 1960.)

[2] Employment and Conditions of Work of Nurses. Geneva: International Labour Office. 1960. Pp. 176. 12s.

[3] Simpson, M. *Lancet*, April 30, 1960, p. 977.

[4] See *ibid.* p. 967.

[5] Feinstein, A. R., Spagnuolo, M. *New Engl. J. Med.* 1960, 262, 533.

[6] Jones, T. D. *J. Amer. med. Ass.* 1944, 126, 481.

[7] American Heart Association. *Mod. Conc. cardiov. Dis.* 1955, 24, 291.

[8] Feinstein, A. R., Di Massa, R. *New Engl. J. Med.* 1959, 260, 1001.

Of the 121 recurrent attacks in 90 patients who had organic murmurs during the first attack, the original murmur persisted in 81, recurred in 34, and was replaced by a different murmur in 6 In 54 of these recurrences fresh cardiac damage became manifest through the appearance of new murmurs, further enlargement of the heart congestive failure, or pericarditis Hence the menace of recurrences was abundantly evident in patients who had had a previous attack during which an organic murmur had been heard On the other hand, the older concept that recurrences are dangerous to *all* patients, including those whose hearts escape damage in the first attack, was not upheld Feinstein and Spagnuolo ascribe this divergence from the traditional idea to their strict criteria for significant heart damage—criteria from which earlier work[8] had led them to exclude prolongation of the P-R or Q-T intervals in electrocardiograms and slight enlargement of the heart As evidence of organic damage to valves they demanded a diastolic murmur audible at the base or left sternal border, or a systolic murmur (with or without a diastolic murmur in the same area) loudest at the apex and transmitted to the axilla In their view it is only because organic murmurs are sometimes missed in first attacks that such murmurs are ever taken to be a new development in a recurrence Aortic diastolic murmurs are particularly liable to be missed in this way

In all, just over 60% of the patients in this series developed organic rheumatic valve disease—a figure similar to that reported from Boston by Bland,[9] who compared the severity of cases of rheumatic fever presenting at different times in the period 1921–51 While the incidence of organic valvular disease remained fairly stable (58–75%), the proportion of cases with severe cardiac enlargement fell during these thirty years from 30% to 14% and the five-year mortality-rate declined even more strikingly from 24% to 3% Coupled with a decrease in incidence this decline in severity has reduced the stature of rheumatic fever as a cause of dangerous illness in children and of chronic cardiac invalidism But as long as group-A streptococci survive in our environment and the pathogenetic link between the organism in the respiratory tract and the damaged valve remains obscure, there can be no certainty that rheumatic fever and rheumatic carditis will continue to dwindle in importance

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[9] Bland, E F *ibid* 1960, 262, 597

TRAINING IN RADIOLOGICAL HEALTH AND SAFETY

THE no 1 pile at Windscale plutonium factory went wrong on Oct 10, 1957, and the investigation of this accident first drew public attention to the national shortage of trained radiological health and safety specialists This shortage was one of the main points emphasised in the report[1] of the Fleck Committee on the organisation for control of health and safety in the United Kingdom Atomic Energy Authority, and the report recommended that the Authority should take the lead in building up the national supply of health and safety specialists A committee, under the chairmanship of Sir Douglas Veale, formerly Registrar of the University of Oxford, was accordingly set up to consider the need for specialists to deal with the health and safety aspects of the use of ionising radiations and radioactive substances The report now published[2] makes recommendations about the types of experts needed and their training, and is at present being studied by the U K Atomic Energy Authority and the Government departments concerned

The report describes the types of work involved in achieving radiological health and safety, and the kinds of training needed It reviews the present position in this country and discusses the responsibilities of Government departments, local and public authorities, hospitals, and the medical profession, and nationalised and private industry An estimate is attempted of the total number of trained people required during the next ten years At the top level, university postgraduate courses have already been established to give a wide training—overlapping the boundaries of medicine, biology, physics, and chemistry —to selected graduates in science or medicine There are courses at London and Birmingham, and the University of Edinburgh plan to start a course in October The committee believe that these courses, fully developed, will meet the need for twenty or thirty top-grade specialists a year The report recommends that similar courses of a less advanced kind should be set up at two or three colleges of advanced technology At a lower level again, a scheme is suggested for introducing certificate courses at technical colleges in the autumn of 1961 Concerning the proposal for a national training centre, the committee consider it unnecessary, and recommend that the existing educational system should be used to provide the sort of training needed

To make the best use of specialists, the report suggests a national radiological advisory service, with regional centres, to be set up under the Minister for Science This service would advise organisations (such as firms making use of radioisotopes) without full-time health and safety specialists of their own It would give expert help in the case of an accident involving possible radioactivity hazards

The report also urges that all medical students should be given some knowledge of radiological health and safety in their undergraduate training, and that a course should be included in the curriculum for the diploma in public health.

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[1] Cmnd 342 H.M Stationery Office, 1958 See *Lancet* 1958, i, 157

[2] Training in Radiological Health and Safety Report of a Committee appointed by the United Kingdom Atomic Energy Authority H.M Stationery Office Pp 95 *5s 6d*

TABLE III—WATER-TOLERANCE TESTS ON SUBJECTS 74 H AND 76 H

Date	Subject 74 H		Subject 76 H	
	Water load (ml.)	Net recovery* (%)	Water load (ml.)	Net recovery* (%)
June 28	1445	38·7	1120	78·4
July 5	1375	20·9	1120	35·2
„ 8	1320	0·0	1065	2·1
„ 10	1345	71·6	1075	11·3
„ 21	1410	94·7	1130	86·5

* Volume of urine passed in four hours from start of test expressed as % of water load after correction for basal urinary flow

of minute urinary volume, and no impairment of vasomotor reflexes (table II) In a water-tolerance test (table III) he began to sweat 8 minutes after starting to drink. The net recovery of the water load was zero At this time, in spite of limited water intake, there had been a fall in the serum osmolarity and hæmatocrit (table IV) The results of this test were remarkable. Subjects on this nutrient regimen with restricted water intake generally show a diuresis as though they were not dehydrated (Sargent et al 1959)

He remained in sick-bay until the next day His nutrient regimen was not altered. During the rest of the experimental period, even though permitted unlimited water, he drank less than 1800 ml. daily Presumably his lack of thirst was due to the pure carbohydrate diet (Sargent et al 1957) Some additional dehydration developed, for on July 11 the hæmatocrit had risen to 46·5%, the maximum value for this man Nevertheless, sweating was normal thereafter

SUBJECT 76 H, white male, aged 18, had a high-protein high-fat ration yielding 1000 kg cal Each day he too marched three miles On July 8, he reported to sick-bay complaining of substernal tightness of 20 hours' duration Examination revealed an oral temperature of 99·6°F, pulse-rate of 144, cervical and axillary lymphadenopathy, total anhidrosis, and pharyngitis He was moderately febrile and had a tachycardia and a relative increase of systolic and diastolic blood-pressure, but his vasomotor reaction to standing was normal (table V) The minute urinary volume was not reduced from previous values of the pre-period (June 27 and July 2) This failure of the minute urinary volume to decrease with limitation of water was caused by the high osmotic content of his nutrient regimen (Sargent et al. 1959) The low minute urinary volume of subject 74 H at this same time was due to the lower osmotic content of the pure carbohydrate regimen

TABLE IV—BIOCHEMICAL MEASUREMENTS ON SUBJECTS 74 H AND 76 H

Date	Serum osmolarity (mOsm per litre)		Hæmatocrit (%)	
	74 H	76 H	74 H	76 H
June 27	291	286	45·3	44·4
July 2	287	292	43·6	44·2
„ 8	272	300	43·0	47·5
„ 11	283	284	46·5	49·0
„ 15	276	282	44·0	47·1
„ 20	282	274	42·6	43·9
„ 25	280	278	45·0	44·0

In a water-tolerance test (table III) only 2·1% of the oral dose was excreted. Within a minute of drinking, sweating began. At the time of the test this subject showed hæmoconcentration —elevated serum osmolarity and hæmatocrit (table IV) This behaviour was quite usual for men on diets with high osmotic content and restricted water

He remained in the sick-bay until July 10, his nutrient regimen was not changed. Sweating continued normally for the rest of the experimental period.

On July 10 he was given another water diuresis test, only 11·3% of the test dose was excreted (table III) After drinking this water, no definite outburst of sweating was detected. One interesting comment, however, was made by the observer 79 minutes after the test began, the left leg was hot and dry while the right leg was cool and damp with perspiration Evidence of hæmoconcentration (elevated hæmatocrit) was still present on July 11 (table IV)

SUBJECT 33 H, white male, aged 18, had a high-protein high-fat ration yielding 1000 kg cal He marched twelve miles a day After 24 hours of this regimen he began to complain of nausea, severe thirst, headache, abdominal pain, precordial pain, weakness, and dizziness 2 days later (July 9) he was brought to the sick-bay complaining of an inability to sweat. He stated that he had felt hot for 36 hours On the day before admission he drank only 1820 ml of water (His allowance was 2730 ml) On the day of admission he had consumed 1820 ml of water up to 4.30 P M On July 9 he had sweated normally in the morning While marching back to camp after lunch, his fellow subjects remarked that his back was dry, even though the hike was done under a hot sun. At this time there was sweat on his forehead He staggered while marching During this march a headache developed and nausea which had started after breakfast persisted He continued to sweat from his forehead until about 4 00 P.M , when all sweating ceased and he became progressively weaker and more dizzy He reported urinary frequency but no polyuria He was an anxious-looking, well-developed, well-nourished young man A sticky sound accompanied his speech The tongue was thickly coated with cafe-au-lait coloured material The skin was hot and completely dry The groin and axillæ were also dry There were no lesions of any kind on the skin The oral temperature was 101·6°F and respiratory rate was 28 The pulse-rate was 100 The lying blood-pressure was 138/80 mm Hg Immediately on standing, the blood-pressure was 100/0 and one minute later while standing the pressure was 105/70 There was hyperreflexia of tendon reflexes

TABLE V—RECORD OF FUNCTIONAL TESTS ON SUBJECT 76 H

Date	Blood-pressure (mm. Hg)		Pulse		Oral temp (°F)	Minute urinary vol. (ml.)
	Lying	Standing	Lying	Standing		
June 27	108/80	100/65	60	100	98·6	0·57
July 2	104/60	108/66	58	112	98·8	0·65
„ 8	130/90	120/80	112	140	100·0	0·62
„ 11	118/44	93/75	64	100	97·6	0·77
„ 15	104/55	96/86	56	84	97·2	0·42
„ 20	118/70	104/93	54	82	98·6	2·33
„ 25	106/70	105/76	68	94	98·6	0·62

He was confined to bed and his nutrient regimen was not altered During the evening he drank some water from his remaining allowance (910 ml) and ate meat bar which caused more nausea and cramps At 10 30 P.M the oral temperature was 99·0°F and total anhidrosis was still present

On July 10, he was given special functional tests The oral temperature was 97·6°F, the lying blood-pressure and pulse-rate 120/64 and 46, and the standing blood-pressure and pulse-rate 110/78 and 64 The minute urinary volume was 0·5 ml per hour He was still anhidrotic.

The decision was made to have him march (quarter-mile laps at 3·75 m.p.h) in the afternoon to see whether sweating could be induced. During the march he was accompanied by a medical officer Sweating did develop, especially on the forehead During the fifth and sixth laps he complained of increasing sense of warmth, pressure on his chest, and dizziness At the end of the sixth lap he was removed from the march The pulse-rate was 148 and the rectal temperature 100·5°F The respiratory rate was 43 He complained of tingling in hands, arms, chest, and mouth A strongly positive Chvostek sign was elicited. 13 minutes later the only sweat was on the forehead. 16 minutes after the end of march paræsthesias of mouth and fingertips continued. At 19 minutes the rectal temperature was 101·4°F and the pulse-rate 76 At 44 minutes they were unchanged. At 46 minutes the tingling had disappeared. At 56 minutes the rectal temperature was 101·0°F and the pulse-rate 54 At 71 minutes the rectal temperature was 100·8°F and the pulse-rate 64 The sweat-loss during the march was 850 ml per hour

He spent the remainder of the day in the sick-bay On July 11 he was released. Normal sweating had been restored.

Special Articles

OBSERVATIONS ON EXPERIMENTAL ANHIDROSIS

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Bannister's (1959) report that 12 soldiers developed total anhidrosis in the absence of miliarial lesions and pyrexia is of profound significance in relation to the pathophysiology of heatstroke. If case-histories can be trusted, many patients experience significant depression of sweating before the onset of hyperpyrexia (Hearne 1919, 1932, Ferris et al. 1938, Austin and Berry 1956). Not infrequently this depression begins a day or two before the heatstroke. One might expect, therefore, to find cases of anhidrosis which had not yet developed hyperpyrexia. Bannister's observations confirm this prediction. We should like to support his observations with an account of anhidrosis induced in volunteers participating in studies on survival rations. Some of this information has been given to the Central Society for Clinical Investigation (Sargent et al. 1956), but the only full report is in Air Force Technical Reports (Sargent et al. 1954, 1957).

At this point a word should be said on how anhidrosis or hypohidrosis was diagnosed among our subjects. At a time when the observer was sweating profusely, the skin of the anhidrotic subject was hot and dry to palpation both over the trunk and extremities and also in the axillæ and groin. The hypohidrotic subject had wide areas of hot dry skin but in other areas sweating could be detected by close inspection or palpation. Although Bannister (1959) does not give his grounds for diagnosis, the implication is that he, too, used clinical examination.

Observations

Experiences of 1953

Between January and June, 1953, a nutritional physiological investigation was made on eight students (Sargent et al. 1954). During a late spring heat-wave one of two men who were on a regimen of restricted water intake developed total anhidrosis.

SUBJECT 8 T, white male, aged 22, began eating a ration which provided 2000 kg cal per day (15% protein, 52% carbohydrate, and 33% fat) on May 25. He was allowed only 900 ml. water daily. On day 3 he complained of thirst, nausea, and depression. On day 4 he was still thirsty, 250 ml. of water was added to the allowance. On day 5 there was aching in legs, pallor, weakness, fatigue, and orthostatic light-headness. On day 6 he reported feeling "lousy", weak, and tired, the tongue was dry and coated, 600 ml. of water was added to the allowance. Late this day pain appeared in the loins and there was tenderness to palpation. Urine specific gravity, 1·034, no albumin, thick mucus, 2–4 leucocytes per low-power field, occasional finely and coarsely granular casts. On day 7 he was nauseated, dizzy, weak, tired, depressed, anorectic, and complained of pain in the loins. The oral temperature was not raised. There was total anhidrosis, but no evidence of miliaria, 195 ml. of urine was passed in 500 minutes (0·39 ml. per min.). Urine was as on day 6. A water-tolerance test was given (Subject drank water load of 20 ml. per kg. bodyweight and urine was collected for 4 hours.) Within the 1st hour he felt dizzy and then exhibited an outburst of profuse sweating. 29% of the oral load was recovered in 4 hours. 4 hours after the start of the water-tolerance test, pitting œdema (+) appeared on lower extremities, next day it had disappeared. Unrestricted water was allowed and recovery was uneventful.

Daily maximum and minimum temperatures (°F) for May 25–31 were 88/67, 89/75, 75/47, 76/52, 90/54, 92/68, 92/69. This heat-wave provoked sweating in all our subjects. Two were on restricted water at this time and both were given extra water to compensate for the sweat-loss. Both complained of severe thirst and one (8 T) developed acute anhidrosis. While our data suggested that 8 T was dehydrated, he was no more dehydrated than the other subject on restricted water who did not develop anhidrosis.

Experiences of 1955

During the months of June and July, 1955, one hundred volunteer airmen were studied in a nutritional physiological investigation at Camp Atterbury, Indiana (Sargent et al. 1957). Forty-four of them had restricted allowances of water for 9 days, and in the first 7 days (July 6–12) there were three cases of total anhidrosis and eight of hypohidrosis among them.

TABLE I—ONSET OF ANHIDROSIS AND HYPOHIDROSIS IN RELATION TO TEMPERATURE AND HUMIDITY

Date of onset	Maximum temp (°F)	4.30 P.M. relative humidity (%)	Number of cases	
			Anhidrosis	Hypohidrosis
July 6	95	46	0	0
„ 7	92	54	0	0
„ 8	93	81	2	1
„ 9	99	81	1	1
„ 10	96	53	0	4
„ 11	94	35	0	1
„ 12	93	34	0	1
„ 13	95	34	0	0
„ 14	90	99	0	0

Table I shows that the temperature exceeded 90°F every day, and that on July 8 and 9 the relative humidity was 81%.

At first each man was allowed only 910 ml. water daily (one canteen). Because of the two cases of anhidrosis and the rapid weight-loss among these men, the allowances were increased on July 8 by one canteen to 1820 ml. for twenty-two men marching three miles a day and by two canteens to 2720 ml. for twenty-two men marching twelve miles a day. The hypohidrosis in some of the men marching three miles a day led to an increase of their allowance to 2720 ml. on July 11.

SUBJECT 74 H, white male, aged 18, had carbohydrate only (2000 kg cal. daily). Each day he walked no more than three miles. On July 8 he complained of weakness, dizziness, occipital headache, and low back pain. (The last two symptoms had been persistent since he arrived at Camp Atterbury and were attributable to anxiety. They cleared rapidly in the recovery period.) Examination revealed a rectal temperature of 99·8°F, hot skin, total anhidrosis (including groin and axillæ), and slightly injected left eardrum. He had mild fever, an elevated pulse-rate both lying and standing, marked reduction

TABLE II—RECORD OF FUNCTIONAL TESTS ON SUBJECT 74 H

Date	Blood-pressure (mm. Hg)		Pulse		Oral temp (°F)	Minute urinary vol. (ml.)
	Lying	Standing	Lying	Standing		
June 27	145/80	142/105	68	96	98·6	2·41
July 2	132/88	110/84	64	100	98·9	0·83
„ 8	135/82	134/90	88	128	100·0	0·25
„ 11	114/64	128/76	62	84	98·0	0·80
„ 15	108/68	129/95	68	108	98·2	0·54
„ 20	106/58	126/100	68	94	98·0	1·82
„ 25	128/66	126/94	62	96	97·8	1·17

TABLE III—WATER-TOLERANCE TESTS ON SUBJECTS 74 H AND 76 H

Date	Subject 74 H		Subject 76 H	
	Water load (ml)	Net recovery* (%)	Water load (ml)	Net recovery* (%)
June 28	1445	38 7	1120	78·4
July 5	1375	20·9	1120	35 2
„ 8	1320	0·0	1065	2 1
„ 10	1345	71·6	1075	11 3
„ 21	1410	94 7	1130	86 5

* Volume of urine passed in four hours from start of test expressed as % of water load after correction for basal urinary flow

of minute urinary volume, and no impairment of vasomotor reflexes (table II) In a water-tolerance test (table III) he began to sweat 8 minutes after starting to drink. The net recovery of the water load was zero At this time, in spite of limited water intake, there had been a fall in the serum osmolarity and hematocrit (table IV) The results of this test were remarkable Subjects on this nutrient regimen with restricted water intake generally show a diuresis as though they were not dehydrated (Sargent et al 1959)

He remained in sick-bay until the next day His nutrient regimen was not altered. During the rest of the experimental period, even though permitted unlimited water, he drank less than 1800 ml daily Presumably his lack of thirst was due to the pure carbohydrate diet (Sargent et al 1957) Some additional dehydration developed, for on July 11 the hæmatocrit had risen to 46 5%, the maximum value for this man. Nevertheless, sweating was normal thereafter

SUBJECT 76 H, white male, aged 18, had a high-protein high-fat ration yielding 1000 kg cal Each day he too marched three miles On July 8, he reported to sick-bay complaining of substernal tightness of 20 hours' duration Examination revealed an oral temperature of 99 6°F, pulse-rate of 144, cervical and axillary lymphadenopathy, total anhidrosis, and pharyngitis He was moderately febrile and had a tachycardia and a relative increase of systolic and diastolic blood-pressure, but his vasomotor reaction to standing was normal (table V) The minute urinary volume was not reduced from previous values of the pre-period (June 27 and July 2) This failure of the minute urinary volume to decrease with limitation of water was caused by the high osmotic content of his nutrient regimen (Sargent et al 1959) The low minute urinary volume of subject 74 H at this same time was due to the lower osmotic content of the pure carbohydrate regimen

TABLE IV—BIOCHEMICAL MEASUREMENTS ON SUBJECTS 74 H AND 76 H

Date	Serum osmolarity (mOsm per litre)		Hæmatocrit (%)	
	74 H	76 H	74 H	76 H
June 27	291	286	45 3	44·4
July 2	287	292	43·6	44 2
„ 8	272	300	43·0	47·5
„ 11	283	284	46·5	49·0
„ 15	276	282	44·0	47 1
„ 20	282	274	42·6	43·9
„ 25	280	278	45·0	44·0

In a water-tolerance test (table III) only 2 1% of the oral dose was excreted Within a minute of drinking, sweating began. At the time of the test this subject showed hæmoconcentration —elevated serum osmolarity and hæmatocrit (table IV) This behaviour was quite usual for men on diets with high osmotic content and restricted water

He remained in the sick-bay until July 10, his nutrient regimen was not changed. Sweating continued normally for the rest of the experimental period

On July 10 he was given another water diuresis test, only 11 3% of the test dose was excreted (table III) After drinking this water, no definite outburst of sweating was detected. One interesting comment, however, was made by the observer 79 minutes after the test began, the left leg was hot and dry while the right leg was cool and damp with perspiration Evidence of hæmoconcentration (elevated hæmatocrit) was still present on July 11 (table IV)

SUBJECT 33 H, white male, aged 18, had a high-protein high-fat ration yielding 1000 kg cal He marched twelve miles a day After 24 hours of this regimen he began to complain of nausea, severe thirst, headache, abdominal pain, precordial pain, weakness, and dizziness 2 days later (July 9) he was brought to the sick-bay complaining of an inability to sweat He stated that he had felt hot for 36 hours On the day before admission he drank only 1820 ml of water (His allowance was 2730 ml) On the day of admission he had consumed 1820 ml of water up to 4 30 P M On July 9 he had sweated normally in the morning While marching back to camp after lunch, his fellow subjects remarked that his back was dry, even though the hike was done under a hot sun At this time there was sweat on his forehead He staggered while marching During this march a headache developed and nausea which had started after breakfast persisted He continued to sweat from his forehead until about 4 00 P M , when all sweating ceased and he became progressively weaker and more dizzy He reported urinary frequency but no polyuria He was an anxious-looking, well-developed, well-nourished young man A sticky sound accompanied his speech The tongue was thickly coated with cafe-au-lait coloured material. The skin was hot and completely dry The groin and axillæ were also dry There were no lesions of any kind on the skin. The oral temperature was 101 6°F and respiratory rate was 28 The pulse-rate was 100 The lying blood-pressure was 138/80 mm Hg Immediately on standing, the blood-pressure was 100/0 and one minute later while standing the pressure was 105/70 There was hyperreflexia of tendon reflexes

TABLE V—RECORD OF FUNCTIONAL TESTS ON SUBJECT 76 H

Date	Blood-pressure (mm. Hg)		Pulse		Oral temp (°F)	Minute urinary vol (ml.)
	Lying	Standing	Lying	Standing		
June 27	108/80	100/65	60	100	98·6	0 57
July 2	104/60	108/66	58	112	98 8	0·65
„ 8	130/90	120/80	112	140	100 0	0 62
„ 11	118/44	93/75	64	100	97 6	0 77
„ 15	104/55	96/86	56	84	97 2	0·42
„ 20	118/70	104/93	54	82	98·6	2 33
„ 25	106/70	105/76	68	94	98·6	0·62

He was confined to bed and his nutrient regimen was not altered During the evening he drank some water from his remaining allowance (910 ml) and ate meat bar which caused more nausea and cramps At 10 30 P.M the oral temperature was 99 0°F and total anhidrosis was still present

On July 10, he was given special functional tests The oral temperature was 97 6°F, the lying blood-pressure and pulse-rate 120/64 and 46, and the standing blood-pressure and pulse-rate 110/78 and 64 The minute urinary volume was 0 5 ml per hour He was still anhidrotic.

The decision was made to have him march (quarter-mile laps at 3 75 m p h) in the afternoon to see whether sweating could be induced During the march he was accompanied by a medical officer Sweating did develop, especially on the forehead During the fifth and sixth laps he complained of increasing sense of warmth, pressure on his chest, and dizziness At the end of the sixth lap he was removed from the march The pulse-rate was 148 and the rectal temperature 100 5°F The respiratory rate was 43 He complained of tingling in hands, arms, chest, and mouth. A strongly positive Chvostek sign was elicited 13 minutes later the only sweat was on the forehead 16 minutes after the end of march paræsthesias of mouth and fingertips continued At 19 minutes the rectal temperature was 101 4°F and the pulse-rate 76 At 44 minutes they were unchanged At 46 minutes the tingling had disappeared At 56 minutes the rectal temperature was 101 0°F and the pulse-rate 54 At 71 minutes the rectal temperature was 100 8°F and the pulse-rate 64 The sweat-loss during the march was 850 ml per hour

He spent the remainder of the day in the sick-bay On July 11 he was released. Normal sweating had been restored

TABLE VI—CLINICAL OBSERVATIONS ON EIGHT CASES OF HYPOHIDROSIS

Subject no	Date of onset	Nutrient regimen	Clinical observations
26 H	July 8	Starvation	White male complained of dizziness, headache, thirst, and *dry skin*
68 H	„ 10	Starvation	Negro male complained of abdominal cramps, drowsiness, *cessation of sweating*, and impending death. Water-tolerance test did not provoke sweating Dry skin continued until July 12, when he was removed from experimental regimen.
70 H	„ 12	Starvation	White male complained of abdominal pain and weakness on July 11 and 12 *Skin dry* and face flushed on July 12 He was removed from experimental regimen.
73 H	„ 9	*0/100/0** *2000*	White male complained of *reduction of sweating* No outburst of sweating during water-tolerance test of July 10
75 H	„ 10	30/0/70* 1000	White male complained of *reduction of sweating* Skin was dry before water-tolerance test. Water load provoked a sweat response
78 H	„ 10	30/0/70* 2000	White male collapsed after marching from camp in afternoon. Examination revealed oral temp of 99 8°F, *hot dry skin with minimal sweating on forehead*, stertorous breathing, and premature ventricular contractions (one per 10 beats) There was an outburst of sweating shortly after beginning to drink water dose.
79 H	„ 10	2/20/78* 1000	White male complained of *reduction of sweating* Sweating began on forehead several minutes after beginning to drink water dose.
82 H	„ 11	2/20/78*	White male complained of arm and leg cramps Skin was pale and *dry*, hyperreflexia of tendon jerks Water dose of preceding night caused moderate outburst of sweating

* Percentage of protein, carbohydrate, and fat over daily caloric intake in kgcal

Of the other men who had been on restricted water allowances, eight developed hypohidrosis They had many of the same prodromal complaints as the three who became anhidrotic (table VI) (Note particularly the record for subjects 68 H and 78 H) In most cases the symptoms came on immediately after the sultry period of July 8 and 9 (table I)

One case of hypohidrosis (26 H) was seen among the men marching twelve miles a day on the day when water allowances were increased for men on restricted water After water allowances for men doing hard work had been increased to 2730 ml daily, no further cases appeared in this group The remaining cases were in men still allowed only 1810 ml —i e , men marching three miles a day On July 10, when four cases of hypohidrosis appeared within this group, each was given a water-tolerance test and the daily water allowance was augmented to 2730 ml After this alteration only two mild cases of hypohidrosis were seen The general appearance and attitudes of all the men improved considerably

Discussion

In these two investigations, four men with total anhidrosis and eight men with hypohidrosis were observed All had been on restricted water, and they showed depression of sweating at a time of heavy demand on the evaporative mechanisms None had significant pyrexia, any evidence of miliaria, or clinical signs of heat exhaustion Of the nine who were given a water-tolerance test, seven sweated freely within a few minutes of beginning to drink No cases of depressed sweating were seen among men allowed unlimited amounts of water, and no new cases developed among men whose allowance was increased from 910 to 2730 ml daily, even though the weather remained hot (table I)

Two questions arise (1) why the marked depression of sweating, and (2) why the outburst of sweating?

Depression of Sweating

The sixteen cases of anhidrosis and eight cases of hypohidrosis reported by Bannister (1959) and ourselves have two characteristics which cast doubt on current concepts of depression of the rate of sweating Since none of the subjects had miliarial lesions, mechanical occlusion of the sweat-ducts by miliaria rubra or profunda (Sargent and Slutsky 1957) can be excluded The anhidrosis of heatstroke is not caused by miliaria (Shelley, Horvath, and Pillsbury 1950) Ladell (1957) has suggested that cessation of sweating in heatstroke is merely a physiological reaction to a raised body temperature, but this view appears untenable Thus suppression of sweating usually precedes the onset of symptoms of heatstroke (Hearne 1919, 1932, Ferris et al 1938, Austin and Berry 1956, Medical Research Council 1958) Our cases of anhidrosis and hypohidrosis, and those of Bannister (1959) were all apyrexial Hence it seems that in both heatstroke and " acute anhidrotic heat exhaustion " the depression of sweating is not due to hyperpyrexia " Exhaustion of the sweating mechanism " was proposed by Hearne (1919, 1932) as the basis of heatstroke, particularly since he was unable to promote sweating with large subcutaneous injections of pilocarpine This attractive hypothesis, however, has not been critically investigated in the climatic chamber, and one can only speculate that " sweat gland fatigue " might be the process common to both these types of depression of sweating

Some investigators (Ladell 1955) report that dehydration depresses sweating, others (Adolph et al 1947) say that it does not Our subjects, like Bannister's, were dehydrated The men with depression of sweating, however, were no more dehydrated than paired controls who did not develop anhidrosis or evident hypohidrosis (Sargent et al 1957) Since no cases of anhidrosis or hypohidrosis were seen in men who were not dehydrated, the facts suggest that dehydration predisposes to these clinical episodes though it does not cause them Perhaps it is for this reason that the literature on dehydration and rate of sweating is conflicting It seems that we simply have not yet defined the true cause for apyrexial anhidrosis and hypohidrosis The idea of " sweat-gland fatigue " does not aid much here, for such depression of sweating can occur in the absence of dehydration (Gerking and Robinson 1946, Thaysen and Schwartz 1955)

Outburst of Sweating

Our experience differs from that of Bannister Whereas our men sweated very soon after drinking, his did not Why he should have not seen this phenomenon is not clear, for it has been observed many times both in the laboratory and in the field (Saito 1930, Lee and Mulder 1935, Adolph et al 1947, Lemaire 1954) even among men who were sweating normally Our impression is that dehydrated men are more apt to show the outburst The mechanism is unknown Kuno (1956) has suggested that it is the result of a gastro-hypothalamic reflex, but his arguments are not convincing Perhaps the drinking-hyperhidrosis is a distinguishing feature of this apyrexial anhidrosis Since the anhidrosis of heatstroke cannot be broken by pilocarpine (Hearne), we are dealing either with different pathophysiological processes or with a less easily reversible stage of a process common to both

Conclusions

These sixteen cases of anhidrosis among men without pyrexia and without miliaria (twelve reported by Bannister, four by us) raise new problems concerning the physiology and pathophysiology of sweating Unravelling them will increase our understanding of the pathogenesis of heatstroke.

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Conference

RESEARCH IN THE CARIBBEAN

THE fifth annual scientific conference organised by the Standing Advisory Committee for Medical Research in the British Caribbean was held at the University College of the West Indies, Jamaica, on April 2–4 The topic for the meeting was the application of the laboratory to problems of clinical medicine. Prof A. C. FRAZER (Birmingham), Prof E T. C SPOONER (London), and Prof G BRAS (U C W I) took the chair in turn.

Cardiovascular Disorders

Hospital studies and field surveys were reported from Jamaica, Trinidad, British Guiana, and St. Kitts by Dr J A. TULLOCH (U C.W I), Dr G WATTLEY (Trinidad), Dr H HAMILTON (British Guiana), and Dr K. L. STUART (U C.W I) Hypertensive heart-disease was the commonest cardiac cause for hospital admission, followed by luetic and then rheumatic heart-disease. Acute rheumatic fever was common and in Trinidad affected the East Indian more than the Negro Cor pulmonale was uncommon in both Trinidad and Jamaica but was seen more often in British Guiana. In British Guiana and Trinidad it occurred almost exclusively in the East Indian. This racial difference could not be satisfactorily explained. Myocardial infarction was uncommon in all the territories This was of interest because aortic atheroma was as common in Jamaica as in the United States of America although coronary-artery atheroma was less severe in Jamaica than in America.

A chest X-ray survey of 3000 people in Barbados showed a 10·7% incidence of cardiovascular abnormality and a considerable proportion had a positive serological test for syphilis Yaws has not been recognised in Barbados for many years This emphasised the fact that symptomless cardiovascular syphilis may be more common than has been thought and poses an important public-health problem. There was an urgent need for a test, serological or otherwise, that would differentiate syphilis from yaws

Hypertension was common and field surveys in Jamaica and St. Kitts by Dr STUART showed that blood-pressures in St. Kitts were slightly higher than those reported by the Medical Research Council team in South Wales, whereas in Jamaica the figures were comparable with those from South Wales Dr Stuart also described an investigation into significant bacilluria in the general population. There was a considerably higher incidence of bacilluria in the hypertensive female and this increased with parity The relationship of bacilluria to hypertension was discussed and the possibility that pyelonephritis was responsible for the greater incidence of hypertension in the elderly female was suggested. A post-mortem study of hypertensive patients did show that renal hypertension was responsible for 50% of the cases and that chronic pyelonephritis accounted for a third of the renal cases

Diabetes Mellitus

Dr TULLOCH said that the prevalence of diabetes in Jamaica was a little over 1% of the adult population, and the ætiology seemed to be very similar to that reported from temperate countries A consideration of the J-type cases by Dr D MACINTOSH (U C.W I) and Dr TULLOCH indicated that this was not a distinct type but was a phase in the natural history of the badly treated type-II patient.

Dr T POON-KING (Trinidad) reported that a considerable proportion of his cases responded satisfactorily to chlorpropamide. The distribution of blood-groups in diabetic subjects was also reported from Trinidad. In both males and females there was a low incidence in group O Males showed an excess of group B and females an excess of group A over the local population as a whole.

Malnutrition

Dr J C. WATERLOW and Dr D I M. PICOU reported preliminary observations from isotope studies in protein malnutrition. The economy of protein was achieved not by a decreased rate of catabolism but by increased reutilisation. Although the extent of protein synthesis might be reduced through shortage of supplies, the capacity for synthesis seemed in most cases to be unimpaired. Magnesium deficiency in malnutrition parallelled potassium deficiency and supported the view that there was a primary loss of intracellular constituents (Dr R. D MONTGOMERY)

Further investigations into the megaloblastic anæmia in malnourished infants were reported by Dr J E MACIVER and Dr E. H. BACK (U C.W.I) They showed that the cause was a dietary deficiency of folic acid, and that vitamin B_{12} was not implicated. Dr MacIver also reported on the nature of the severe anæmic episodes in sickle-cell disease and showed that these were of two types In one folic-acid deficiency was the ætiological factor and in the other there was an acute aplastic state He suggested a possible relationship of the aplastic state to preceding infection.

Non-addisonian vitamin-B_{12} deficiency in the adult was reported from Trinidad by Dr G HABIB. All the patients were Hindus and with one exception they were strict vegetarians eating no eggs, meat, fowl, or fish. Poverty and a vegetarian diet seemed to combine to produce this deficiency state

Dr C. G MILLER (U C.W I) had found hepatomegaly in about 95% of all apparently healthy children under the age of 12 years It was not related to malnutrition but the possible role of infection was considered. The necropsy incidence of cirrhosis of the liver as noted at the University College Hospital of the West Indies was much the same as in America A third of all cirrhosis resulted from veno-occlusive disease of the liver

Neurological Disorders

Dr MONTGOMERY discussed the possibility that the unusual spastic neuropathies seen in Jamaica were related to treponemal infection The neuropathy might be a late manifestation of treponemal infection, venereal or otherwise, and it might be due to a strain acting as a poor antigenic stimulus but producing a typical meningovascular lesion in the nervous system. A second neurological disorder in Jamaica, spinal arachnoiditis, was reported by Prof E. K. CRUICKSHANK and Dr P E RODGERS (U C.W I) The ætiology was largely unknown but it had been found that cases seen early in the disease responded well to cortisone

In England Now

A Running Commentary by Peripatetic Correspondents

DIALOGUE OF TOMORROW

SIR, can you tell me the meaning of an obsolete word? I know medical history is a hobby of yours

I'll try What word?

Auscultation

It meant listening

Listening to what, Sir?

Sounds made by the human body I thought you'd be puzzled Doctors used to listen to their patients' bodies, and palpate them directly, too

Directly? You mean they used some simpler kind of palpating machine than ours?

No, really directly . I see I'll have to demonstrate Come here Put your hand on *my wrist—right on it, skin to skin*

May I really, Sir?

Yes, yes no-one's looking Now in the old days, if you were the doctor and I the patient, that would have been the usual thing Television wasn't used in medicine at all, you wouldn't have been lying in your helicopter, you'd have been sitting close by your patient, probably in his home

Sitting? Home?

Let's leave those words for another time, and return to auscultation Doctors used to listen to the air going in and out of their patients' lungs, and the heart valves opening and closing

How could they *hear* such things?

The world was virtually silent Ancient literature is full of references to people's hearing the songs of birds and the cries of infants, and most authorities believe that such sounds literally were heard The loudspeakers used to be turned off at night Much of the Earth's surface was not even wired for sound Probably everyone spoke much more quietly, and the way we are talking now would have been called shouting

Shouting?

Speaking more loudly than is necessary

But it is always necessary—

—To speak as loudly as possible Yes, but it used not to be What is more, in order to hear the lung sounds and heart sounds better, doctors used something called a stethoscope

What was that like?

Nobody knows

Is it true, Sir, that in those days patients used to do much better?

Do much better?

I mean, for example, was the recovery-rate from acute infections and trauma much higher? Did far fewer patients die in hospital?

It is quite true, and the reason is simple Microorganisms were much less virulent then

And what about trauma?

It used to be much less violent No other explanation is possible

How do you know all this, Sir?

Between ourselves, I've learnt to read I know it's frowned on as taking up time which ought to be spent on listening and learning, and certainly you young fellows have enough to listen to, but you'd be surprised what interesting things have never been electronically recorded

Can you write, too, Sir?

Aha, my boy, now you're pulling my leg

* * *

When I decided to become a plastic surgeon (which was after I had decided to become a general practitioner rather than a psychiatrist, and before I decided to become an anæsthetist) I bought a special needle-holder and forceps Anyone who has learnt to suture a wound with these tools will be unhappy using others, and they are useful in almost any medical career Thus when I was sent, soon afterwards, by one of the Armed Services to the Middle East as Medical Officer With Special Training in Tropical Medicine (my capitals) I found my instruments useful in the treatment of men who had fallen foul of tent-pegs in the dark and of officers who had fallen foul of each other in the officers'-mess bar Later I decided to become a cardiologist, and was appointed resident at Johns Hopkins This turned out to be not Johns Hopkins in Baltimore but Johns Hopkins Memorial Agricultural College Students' Infirmary (their capitals) in a remote State in the Middle West. My instruments were here very useful in the treatment of skiing and skating injuries, and (in the brief summer) after lacrosse matches with the local Apaches I then decided to become a writer, and I must confess that my instruments lay idle while I wore out several typewriters on my great gothic novel, but when the typescript was complete I found the forceps indispensable in getting the tape that was meant to hold the pages together to go through the tunnel formed by the tiny holes I had punched in each page (if any publisher happens to read this, I am still ready to consider offers for my novel) Then I decided to become a radiologist, and polished up my instruments again in the expectation of being able to sew up the skin after cutting down on an artery to perform an angiogram, but my ideas were outdated, for today percutaneous puncture is preferred to a cut-down, and even this (in the highly specialised country where I am being trained) is done by a surgeon, not a radiologist. So for the present my well-made, well cared-for, and experienced instruments are resting (if any young plastic surgeon, not yet fully equipped, chances to read this)

* * *

The representative of the drug firm had a bad cold caught a couple of counties away, but, alas and alack, he had given away the last of his cold-curing samples just before the prodromal symptoms appeared This was particularly sad, for his preparation of some new stuff—plus quinine, faith, and hope—would undoubtedly have prevented, aborted, cut short, or at least minimised to a triviality his streamer Scrabbling in the drawer where I keep the samples left by his colleagues I was lucky enough to find the very wonder-worker he was talking about, neglected since his last visit I handed it back as a practical expression of my sympathy, accompanied by my good wishes for a speedy recovery He accepted it with a rueful laugh, and, entering into the spirit of the thing, watched while I ferreted out eleven other preparations to suck, sniff, squirt, ingest, or inhale—all highly spoken of by their compounders for their efficacy in his malady He tucked them all into his bag saying that it would be something to talk about at the next meeting of his firm's reps —assuming, of course, that he recovered

* * *

From a coloured reproduction on sale at the National Gallery
Dürer, Albrecht (1471–1528)—The Painter's Father (before cleaning)

* * *

"Here's a stout little fellow sticking out all on his very own." His comb smartly tapped my polished cranium. Then his tune changed from the jocular to the regretful, "Dreadful. Oh, dear God, no Ah no, broken off in his prime. Sheer murder No life at all" Scissors and comb were placed with final emphasis by the basin "Doctors [obviously he had spotted my pocket thermometer] should take more care of their appearance All professional men should" "Well, I've still got my own teeth and don't wear glasses," I parried, staring below the level of his healthy glossy thatch into his rimless thick pebbles and the obvious upper and lower acrylics But he went on reproachfully, "I could have helped long ago, perhaps, but of course a tight hat band——" "I never wear a hat." "That's the trouble You should have worn a hat without a tight——" "I thought you said I had a tight scalp" "Never Your scalp is loose, very loose [He was confusing me now] I said massage in your case would be a disaster Breaks those tender little shoots You massaged? Now all you've got is some fluff" He painlessly plucked a wilting but living hair from my occipital area He was gaining the upper hand. "I never massaged. I spent a lot of time and money putting muck on." He raised his wispy eyebrows "You rubbed it in?" "I certainly did." Triumphantly "That's MASSAGE I can see, sir, you need help, for instance I'm not ashamed to wear a mat." "What on earth——?" "A toupé, or rug as we call it in the trade, would suit you. All right, you don't want to be helped. Pity Good day, sir Thank you, sir"

* * *

The world is so full of a number of things
That I loathe the whole lot when the telephone rings.

Letters to the Editor

TROPICAL EOSINOPHILIA

SIR,—Those who are interested in filariasis have, for some time past. been impressed by the gradual and progressive unravelling of the basic ætiology of tropical eosinophilia

The paper by Professor Webb and his colleagues in your issue of April 16 has taken us a long way to the solving of this problem, and in this solution the workers are to be congratulated. It therefore has now been definitely established that the common type of tropical eosinophilia is really a form of filariasis, most probably of zoonotic origin, and that, on this account, this entity becomes the prototype of what P C Beaver has so aptly termed visceral larva migrans

As one who has been interested in the pathology of human filariasis for many years, may I comment upon the excellent photomicrographs which illuminate the paper in question?

They illustrate the cell-aggregation which constitutes the cell picture of human somatic filariasis and agree almost exactly with similar preparations made by T J Danaraj [1] so that this combination of granuloma, eosinophil aggregation, epithelioid and giant cells, together with the hyaline acidophilic substance, referred to as M.K. (Meyers-Kouwenaar) bodies, constitutes the hallmark of filarial lesions in the lungs, liver, and lymph-nodes in the human body These may now be taken as indicating the graveyards of embryonic and adult filariæ in the tissues and should be identified as such in the future There is a cell-aggregation peculiar to filariasis, just as has been established for tuberculosis and leprosy

May I be permitted to point out that this cell picture was originally described and figured by me in my *Report on Filariasis and Elephantiasis in Fiji* in 1912 (plates XXV, XXVIII, and XXXII) At that time it was thought that the cellular response was a reaction to the presence of the adult *Wuchereria bancrofti*, especially when defunct and calcified.

Subsequently, O'Connor and Hulse [2] in 1935 found that this reaction was provoked by dying or recently defunct microfilariæ in the lymph-nodes and other tissues, and their pathological preparations of the typical reaction produced by the embryo and adult filariæ have never been surpassed. They did not differentiate between the cell reactions in both cases

Delving into the records of the past it is obvious that the best and most minute description of the pathology of human filariasis is to be found in the very excellent study by Wartman [3] in 1947 (Filariasis in American Armed Forces in World War II) The detailed descriptions of the pathological findings in biopsies from various sites occupy some 61 pages and remain undoubtedly the best ever produced. Some attention is paid to a comparison of tissue reactions associated with the presence of adult filariæ and that of the embryonic forms, or microfilariæ. In the former instance there is precipitation of strikingly acidophilic material around the remains of the worm with necrosis of tissue, exudation of eosinophils, plasma cells, lymphocytes, proliferation of macrophages and reticular fibres In the case of microfilariæ, either defunct or calcified in the tissues, there is no necrosis and the precipitate around the embryos, when it occurs, is amphoteric. Œdema is conspicuous and the exudate consists chiefly of eosinophils Macrophage and giant cells, although present, are not numerous and there is only slight reticular hyperplasia

It can readily be realised that there exists a mass of long-standing observations which support the pathological evidence put forward by Professor Webb and his colleagues

London W 1 PHILIP MANSON-BAHR.

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1 Danaraj, T J *Amer J trop Med Hyg* 1959, 8, 151
2. O Connor, F W, Hulse, C. R. *Puerto Rico J publ Hlth Trop Med* 1935, 2, 167
3 Wartman, W B *Medicine* 1947, 26, 333

PLACENTA PRÆVIA

SIR,—In his admirable paper of Feb 27 Professor Macafee refers to my condemnation of the use of Willett's scalp forceps in treatment

In my paper [1] I reported two cases of maternal infection by the Welch bacillus, one of them fatal, following its use. I stated that "the risk increases with the length of time elapsing between the application of the forceps and delivery" and that "possibly if delivery took place within an hour or two of the application there would be little danger" One can only be reasonably sure that delivery will take place "within an hour or two" if the patient is in labour and the os dilating before artificial rupture of the membranes is done. Rupture of the forewaters plus a fundal binder will then generally allow the presenting part to be pushed down on to the bleeding point by the contracting uterus alone. This point is important as it is only during a contraction that bleeding in placenta prævia occurs If this does not stop bleeding then I am all in favour of applying Willett's forceps and gentle traction on the forceps if and when bleeding recurs, and have advocated that in my book *Ante-natal and Post-natal Care* If the membranes are ruptured artificially before labour starts the patient may not go into labour for some days even with the help of an oxytocin drip

I do not think it necessary to terminate pregnancy routinely in cases of antepartum hæmorrhage at the 37th or 38th week, as Professor Macafee advises I have always allowed these patients to go into labour spontaneously and have never had cause to regret doing so This non-interference reduces the number of cæsarean sections and premature babies, and tends to prevent the difficulties that Professor Macafee has met with during the lower segment operation—namely, a poorly developed lower uterine segment "behind the symphysis making its exposure difficult" I strongly advise letting patients with antepartum hæmorrhage continue their pregnancy till the spontaneous onset of labour unless, of course, severe bleeding starts or persists, which at any time in pregnancy contra-indicates expectant treatment or its continuation.

I fully support Professor Macafee in his rejection of the use of placentography in antepartum hæmorrhage. After all he got his unequalled results in placenta prævia without its use

Sydney F J BROWNE.

SIR,—It was interesting to read Mr Theobald's letter (April 23) recounting his experiences of obstetrics with drastic restriction in the use of X-rays His excellent figures pay tribute probably more to his considerable clinical skill and experience and overall direction than to any one particular technique, giving support to the contention that it is not so much what is done as by whom it is done that matters Yet surely it is far too early after only nineteen months to say whether or not the complete abandonment of skilled obstetric radiology is good policy in the long run

It is true that in the past few years there has been concern about the possible risks of antenatal X-rays and I think most obstetricians, quite rightly, took the opportunity of reducing unnecessary radiography Now that all the evidence is against such risks with ordinary care, it is surely out of place to try to perpetuate what, after all, was a temporary precautionary measure. It would be a tragedy if all that has been done for obstetrics by radiology were lost and the training of obstetric radiologists abandoned because of this temporary scare

Mr Theobald has lost no mothers from omitting placentography and pelvimetry and he "does not think" he has lost any babies It is a pity he is not able to be precise on this point, for it is really in helping to reduce the *fœtal* risk that obstetric radiology can play such a big part in making breech and forceps deliveries safer, in diagnosing placenta prævia in the *ante* hæmorrhage stage and so helping expectant management for the

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1 *Proc. R Soc. Med.* 1930 32, 1209

sake of the fœtus, in quickly freeing antenatal beds in mild *antepartum hæmorrhage cases so that pre-eclamptic toxæmia* can be treated properly and add to the chances of the fœtus Again, when it was decided to give up radiography we are not told what new safeguards had to be taken—more routine work thrown on the consultant, more patients occupying precious obstetric beds, perhaps more transfusions It is the precise answer to these issues that is needed before a strong argument can be put for the wholesale abandonment of radiography

There is no doubt that in the recent past too many patients were being X-rayed, but reason should now prevail and allow selective radiography to continue playing its important part in the advancement of obstetrics

The London Hospital,
London, E 1

ROBERT PERCIVAL
STANLEY MURRAY

ADDICTION TO DRUGS

SIR,—Your annotation of March 12 quotes the greatly respected American authority Dr Harris Isbell The opening statement, a reference to 50,000 drug addicts in New York City *alone*, may be misleading

The best available evidence indicates that that is a considerable overstatement The opiate addiction count is perhaps not more than 25,000 in New York City Furthermore, a statement of addiction count in New York is likely to give a mistaken impression of the nationwide problem here The addict count in New York may be little better indication of the addiction problem as a whole in this country than is the 150,000 to 250,000 addict count in Hong Kong a reflection of the addiction situation which might exist in the United Kingdom

Opiate addiction in the United States of America is now confined pretty generally to the States of New York, California, Illinois, and Michigan, and the total addict count is perhaps somewhat less than 60,000 We stress this because American narcotic law enforcement is being plagued with a rash of publicity to the effect that in England, which never had a narcotic problem of consequence—even in the early 1920s when 1 out of every 400 Americans was addicted—there is the answer to our narcotic problem England is being cited as possessing some magic alchemy for the control of narcotic addiction, all this to the derogation of the American attempts to control its narcotic problem

The statement is being freely made here—and apparently through repetition it has achieved some acceptability—that the United Kingdom has no opiate problem because there narcotics are freely dispensed by doctors to all askers[1]

M L HARNEY
Formerly Assistant to U S Commissioner of
Narcotics, Assistant to Secretary,
U S Treasury, for Law Enforcement,
Superintendent, Illinois Division
of Narcotic Control

Washington, D C

ADENOVIRUS TYPE-15 INFECTION

SIR,—We were very interested in Dr Duncan's letter of April 9 on the isolation of adenovirus type-15 from 2 patients in Great Britain, since virus strains of this type were also isolated from 3 patients in The Netherlands

A 4-year-old girl who was admitted to this hospital in January, 1957, with relapsing cystitis, developed a febrile pharyngitis two weeks after admission Adenovirus type-15 was isolated from her fæces obtained on the fourth day of the respiratory illness [1] The isolation was made in cultures of HeLa cells Serum specimens were collected on the second day of illness and five weeks later The patient showed a 16-fold increase in complement-fixing antibody against adenovirus type-4 No neutralising antibody for the prototype strain of adenovirus type-15 could be detected either in the acute serum specimen or in the convalescent specimen However, a significant (128-fold) rise in neutralising antibody against the patient's own virus strain was found Three rabbits were immunised with the prototype strain of type-15 and 3 rabbits with the strain isolated in this laboratory The rabbit antisera showed reciprocal cross-neutralisation against both these viruses, but the neutralisation titres against the new strain were always greater (4 to 16 times) than those against the prototype strain

The second patient from whom the virus was isolated in this laboratory was an 8-year-old girl who was operated on for appendicitis in January, 1958 A macroscopically normal appendix was removed Signs of a previous ulcerative inflammation were observed on pathological examination Fragments of appendix tissue were cultivated in test-tubes and showed a cytopathological effect after an incubation period of about four weeks The cytopathological agent was identified as adenovirus type-15

In January, 1959, an adenovirus was isolated by Dr J G Kapsenberg in Utrecht from the stool of a 2-year-old girl suffering from mumps meningoencephalitis The strain was sent to us to be typed and was found to be type-15

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R K University,
St Elisabeth-Hospital,
Tilburg, The Netherlands

J VAN DER VEEN
G VAN DER PLOEG

EXPIRED-AIR RESUSCITATION

SIR,—Thanks to addresses and articles such as those published recently in *The Lancet* and other journals in this country, in the United States, and in Scandinavia, " mouth-to-mouth breathing ", or to use a more euphonious term, expired-air ventilation, has made an impressive return to favour

But, as so often, what appears to be excellent to some causes a clear, and at times almost violent, reaction in others There are, of course, many problems associated with the looked-for introduction of a really effective method of artificial respiration, such as expired-air ventilation seems to be Among the criticisms often heard are the following

(1) *The supine position* —Anæsthetists tremble lest the airway becomes obstructed with a patient lying prone, yet laymen are invited to believe that it is readily maintained in such methods as the Holger-Neilsen As experts have said, however, the arms can too easily slip from under the forehead, and thus lead to airway obstruction Strongly in favour of any position other than prone is that a movement of the chest can be seen by a rescuer, thus there is a constant check of the efficiency of the breathing

(2) *Air is blown into the stomach* —This rarely occurs if the airway is clear and the pressure less than 20 cm of water furthermore it is no great hazard, as it can be readily expressed

(3) *Unhygienic* —Surely yes! If the would-be rescuer has some foul infection of mouth or lungs, *it may* possibly be transmitted this calls rather for selection of first-aid personnel than a wholesale condemnation of the method We do not ban barbiturates because a collection of the capsules is so fondly cherished by would-be suicides

(4) *Unæsthetic* —So was going into the road with a dust pan and brush to collect manure for the garden That was for the garden this may save a child's life

(5) *The rescuer's carbon-dioxide falls* —Further experiments are being undertaken to verify that many people can greatly increase their minute volume without dizziness so long as they deepen and slow respiration This calls for training (see below)

(6) *Instrumentation* —Anæsthetists do not *always* choose the right size of airway from the wide range available! So the long anæsthetic type of airway should not be offered to first-aid personnel Shortened airways, mouth props, rebreathing tubes with one-way valves, and so on are being introduced and may well be of real value for training purposes and for the use of experienced rescue teams Simplicity and speed must ever be

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[1] van der Ploeg G Infecties met adeno-virussen bij kinderen Thesis, Nijmegen, 1959

the keynotes of success, valuable time may be lost while trying to find and fit a standard airway into a substandard mouth!

(7) *Training cannot be done*.—The essence of all methods of artificial respiration is to obtain and maintain a clear airway so that the adequate air can be made to pass into and out of the lungs. Surely techniques of training method can be worked out, short of the actual breathing into the victim. This is indeed the "difficult which can (and should be) done immediately." The impossible—practice manikins—will take a little longer. It is hoped that good-quality manikins will soon become available as it appears that they must form an integral part in any comprehensive training scheme.

In conclusion, I would quote from a letter recently received: "There are drawbacks to mouth-to-mouth breathing, there are advantages in the Holger-Neilsen, but it seems to me that there is one vital difference between the two methods—Holger-Neilsen does not work, mouth-to-mouth does."

Barnet General Hospital,
Barnet, Herts.
ERIC K. GARDNER

HÆMOGLOBIN STANDARD

SIR,—The letter by Dr. Stallybrass (April 16) calls for some comment.

First, no Commission can standardise the iron content of hæmoglobin. This is a quantity which is determined by practical experiment, and for human hæmoglobin, the majority of results obtained by professional scientists lie between the limits of 0·335% and 0·338% of iron in the compound.

Secondly, any Commission is entitled to express its opinion on the relative merits of the various results, but one which gave a recommendation that "100% Haldane became equivalent to an iron content of 14·6 g. per 100 ml." should be sent to the local cat's home with a shilling in its pocket. Apart from the confusion between "content" and "concentration" which is so commonly made that it almost passes as correct nowadays, it has apparently failed to realise the difference between a concentration of *iron* and a concentration of *hæmoglobin*.

Thirdly, the expressing of hæmoglobin concentrations as a "% Haldane" (or as a % anything else) is a very ancient method of recording chemical analyses. We still retain it as an old friend, in the same way that we continue to give a "quarter of morphine" instead of the more "refined" 16·2 mg. of that chemical.

Finally, the expression "100% hæmoglobin" can mean anything that one wants it to mean. No individual or Commission can lay down the law on the matter. It means one thing in Edinburgh, another thing in Lagos. But what is far more important is that "100% hæmoglobin" differs vastly between the two sexes in adult subjects, and this difference is almost invariably ignored. If "100% hæmoglobin" for males is taken as 14·8 g. hæmoglobin per 100 ml. blood, then "100% hæmoglobin" for females will be about 13·3 g. per 100 ml. This is unfortunate, but true.

Department of Biochemistry,
Western Infirmary,
Glasgow.
E. B. HENDRY

*** Dr. Stallybrass' last sentence should have read "... what pathologist can afford knowingly to expose himself either to the charge of individualism, or of nonconformity, or even (if it must be said) of being behind the times?" This appeared as "... the pathologist cannot afford ..." and we apologise to him for this unintentional change. We showed him Dr. Hendry's letter and his reply follows.—ED. L.

SIR,—The purpose of my letter was to draw attention to the fact that 100% Haldane may be equivalent either to 14·6 or 14·8 g. hæmoglobin per 100 ml. of blood. It was my intention to be uncritical of others, and perhaps for this reason I failed to be sufficiently critical of myself: this is the explanation of the regrettable confusion in my introductory paragraph, where the iron content of pure hæmoglobin and the hæmoglobin concentration of blood seem to reflect on the wisdom of the Protein Commission, thereby exposing it to frivolous ridicule.

Also, my letter failed to convey the sense (and this error was not my own) that individualism, &c., could be valuable characteristics, and that resistance to change in a rapidly changing world did not in principle meet with my disapproval.

Hertford County Hospital,
Hertford.
F. C. STALLYBRASS

SPINAL INJURY INVOLVING THE JEJUNUM

SIR,—Rupture of the aorta may result from hyperextension injuries of the lumbar spine and has been described by Lichtblau and Wilson[1] after manipulation of the spine in the treatment of ankylosing spondylitis. They also described a case in which a lumbar intervertebral disc space was opened by 2·5 cm. as determined by radiology, without serious sequelæ. In the case reported below a violent hyperextension injury opened a lumbar disc space so far that a loop of bowel was trapped between the vertebral bodies.

A motor-cyclist aged 17 years attempted to take a right-hand bend at a speed estimated to be about 50 miles per hour. He made some error of judgment and lost control of his machine. He was thrown through the air and it is thought that he may have struck the stay wire of a nearby telegraph pole. He complained to helpers of severe generalised pain and died a few minutes after the accident.

Necropsy findings.—There was a general appearance of exsanguination and multiple abrasions on the limbs and face. There was a linear abrasion in the lumbar region which ran diagonally across the back. There was a compound fracture of the left external malleolus but no other fracture in the limbs. No abnormalities were found in the head, neck, or thorax. His head had been protected by a crash helmet. The peritoneal cavity was full of blood but there was no rupture of any of the intra-abdominal viscera. On attempting to remove the bowel it was found that a loop of jejunum, about 18 in. (45 cm.) from the end of the duodenum, was gripped between the bodies of the third and fourth lumbar vertebræ. The loop ran mainly through the left side of the intervertebral space. The fracture line was perfectly transverse and was at the level of the upper border of the intervertebral disc. At this level there was a complete transverse rupture of the anterior longitudinal ligament, and the psoas muscles had been avulsed from their origins. The inferior vena cava was intact but the adventitia of the aorta showed a considerable extravasation of blood throughout its abdominal course. There was no loss of continuity of the aorta, but the left renal artery had been torn off at its origin leaving a large deficiency.

This injury was probably caused by hyperextension and flexion to the right. The abrasion on the back and the evidence of more violent disruption on the left side of the body supported this view. The hyperextension must have torn the anterior longitudinal ligament allowing wide opening of the disc space. The aorta may have been saved from complete rupture by slipping to the right of the vertebral bodies. This would increase the likelihood of damage to the left renal artery. The stretched anterior abdominal wall, forcing the intestines against the posterior abdominal wall, caused the loop of bowel to be trapped between the vertebral bodies as they came together again. Death followed from massive hæmorrhage.

I wish to thank the Director-General, R.A.F. Medical Services, for permission to publish this case and Air Commodore W. P. Stamm for reading the manuscript.

Royal Air Force Hospital,
Wroughton.
A. KENNEDY

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1. Lichtblau, P. O., Wilson, P. D. *J. Bone Jt Surg.* 1956, 38A, 123.

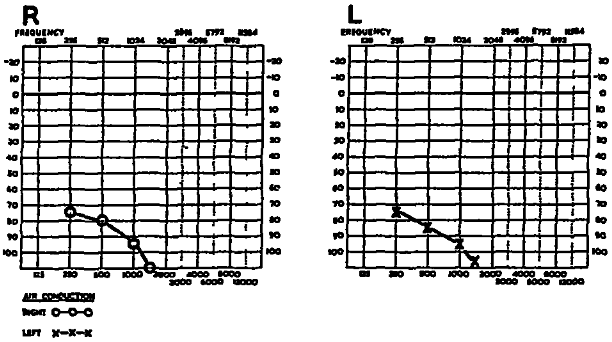
OTOTOXICITY OF NEOMYCIN AEROSOL

SIR,—Shortly after neomycin was introduced in 1949 [1] its toxic effect on the cochlea was described [2 3] Damage to the cochlea followed systemic therapy particularly when there was renal dysfunction or concomitant damage to the kidney parenchyma No case of deafness has been reported after topical application of neomycin Costa [4] reported experimental observations on guineapigs treated with neomycin both systemically and by intranasal instillation, he only found cochlea damage in those given systemic neomycin.

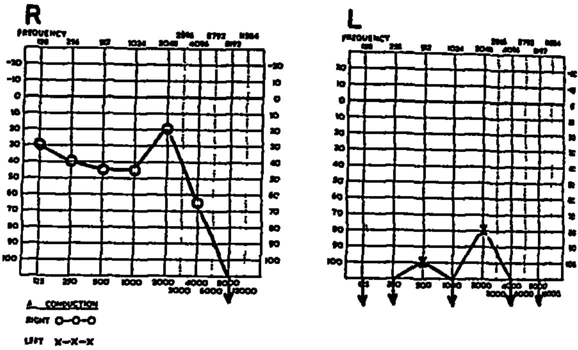
The toxic action is confined to the cochlea Experimentally it comprised atrophy or destruction of the organ of Corti [5] and degeneration of the stria vascularis and cochlea ganglion [6], severe impairment of hearing was also demonstrated in animals without pathological changes in the organ of Corti

Ototoxic damage usually follows long-continued treatment, but it has arisen within 8 days [2] In the two following cases deafness developed after neomycin aerosol had been given for 28 and 18 months. The deafness increases the longer neomycin therapy is continued, and unfortunately it tends to exert its action after the drug has been discontinued [7 8]

CASE 1 —A girl, now aged 5 years, had been found at the age of 12 months to have cystic fibrosis associated with a persistent pulmonary staphylococcal infection, sensitive only to neomycin This was given in aerosol form for 6 weeks when she was 21 months old, and for 28 months a year later Deafness was first noticed at $4^1/_2$ years and it increased rapidly during the next 3 months Until the deafness began her speech developed normally, it then degenerated rapidly into babbling, with a discordant voice The upper respiratory tract showed no abnormality Audiometry after conditioning showed a severe bilateral perceptive deafness, only low tones being heard at 80 decibels (fig 1) This child needs special auditory training with a suitable hearing-aid



CASE 2 —A girl, now aged 9 years, was found to have cystic fibrosis at 5 weeks Localised pulmonary disease predisposing to bronchiectasis was noticed at 4 years 9 months She, too, had a persistent staphylococcal infection sensitive only to neomycin She was treated with neomycin aerosol for 2 weeks at 5 years, 3 weeks at 6 years, 7 months at 7 years, and for 18 months at 8 years Deafness was first noticed 6 months after the last course of neomycin aerosol was started, and was worse in the left ear Her speech changed, becoming more raucous, with elided sibilants The upper respiratory tract was normal Audiometry revealed no hearing in her left ear, and very severe high-tone perceptive deafness in the right ear (fig 2) The hope of this child retaining her speech is greater than in case 1, because she is older and had acquired more speech before she became deaf She has at present more useful hearing than has case 1



I wish to thank Mr N Asherson for permission to describe these cases, and Dr L Fisch of the audiology unit for assistance in their examination

Royal National Throat, Nose
and Ear Hospital,
Gray's Inn Road, London, W C 1

ALAN FULLER.

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[2] Waisbren, B A, Spink, W W *Ann intern Med* 1950, 33, 1099
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NOTIFICATION OF UNSUCCESSFUL CANDIDATES

SIR,—Is there any reason why boards of governors and regional hospital boards should not tell candidates for appointments that they have not been short-listed as soon as this is known?

The common practice at present seems to be to wait until the appointment has been made before telling those candidates who were not interviewed that they have been unsuccessful This practice results in prolonged doubt and anxiety for applicants which a little thoughtfulness could lessen Sometimes other decisions, such as whether to apply for another job, may hang upon the result of an application, and if a man knows promptly that he has not been short-listed he can plan his affairs accordingly

I write not out of a sense of personal grievance but because I have seen friends suffer emotional stress unnecessarily

SUCCESSFUL APPLICANT

INTERMITTENT POSITIVE-PRESSURE RESPIRATION IN INTRACTABLE STATUS ASTHMATICUS

SIR,—I congratulate Dr Broom (April 23) on the successful resuscitation of the two cases of severe status asthmaticus

I notice, however, from the case-history that both patients were given *on admission* intramuscular injections of chlorpromazine and promethazine, supplemented in one case by intramuscular pethidine Three hours later one of the patients is reported as being " well sedated " Four hours later the patient was moribund The other patient's condition deteriorated some two hours after the initial sedation and further chlorpromazine and promethazine was given for restlessness after another two hours Four hours later the patient collapsed and became moribund

I have always felt that the acknowledged ill-effects of opiates in patients with severe bronchospasm resulted not only from *depression of the respiratory centre,* but even more so from the induction of a dangerous mental state of " couldn't care less ", with loss of will to fight for breath and to cough up sputum at the appropriate time

Chlorpromazine and promethazine must induce just this mental state It is difficult not to suspect that the sedatives contributed to the serious deterioration of the patients' state and that it would have been wiser to delay their use until bronchospasm was further relieved or at least to have used smaller doses

Finally it would be instructive to know if the three cases of fatal asthma mentioned were also given the same initial sedation The problem is an important and vital one

It is hoped that the queries raised in this letter will be accepted as a constructive criticism, not a destructive one

The Radcliffe Infirmary, Oxford E M BUZZARD

MEANING OF ANALGESIA

SIR,—I should like to make a plea that the word "analgesia" should be used to indicate what its origin clearly suggests—relief of pain Its use to describe a block of nerves within the dura mater has for some time seemed awkward and leads to remarks such as "an alternative form of anæsthesia is spinal analgesia" and so on Nerves that are adequately blocked cease to transmit all sensations, not only those of pain

But much more serious is the misuse of the word to cover all the drugs that are given to ease the pains of labour Under the term "obstetric analgesia" one finds descriptions of all sorts of drugs, many having no analgesic properties Drugs such as, for example, tranquillisers may make a mother feel better, they may make her feel worse There are some mothers who, though they welcome analgesia, dislike very much the feeling of dissociation, of losing possession of themselves, which such drugs may produce It is possible to stretch a point and say that tranquillisers can in some cases relieve mental pain Equally, they can block an approach to the causes of this pain In any case, in order to use drugs most effectively for easing pain in labour the administrator should be reasonably clear in his mind what actions he is expecting from them

University College Obstetric Hospital,
London, W C 1 SHILA RANSOM

"ELECTROPHEROGRAM"

SIR,—Gerrits et al [1] have referred to "some deviations of the serum-protein spectrum and curve (electropherogram) in patients with pulmonary carcinoma"

The word "electropherogram" as used by these authors appears to mean the densitometric or colorimetric pattern obtained from filterpaper strips on which serum has been electrophoretically separated and stained Such connotation is not universal since other investigators [2] also refer to stained electrophoretic strips as "electropherograms" In addition, there is a lack of uniformity in the spelling of apparently the same term Talluto et al [3] use the word "electrophoreogram" while Zak et al [4] discuss the stained pattern of an "electrophoretogram" Furthermore, other workers have shortened the expression to "pherogram" [5] or "electrogram" [6]

This term as used in the literature can designate a number of different products of the electrophoretic process which are by no means equivalent When the word "electropherogram" or a variation thereof is used, a definition should be included in the text to avoid ambiguity The value of terminology per se depends largely on its specificity Therefore, to prevent confusion the formulation of a more definitive nomenclature pertaining to electrophoresis may be indicated

Departments of Pathology,
Los Angeles County Osteopathic Hospital,
College of Osteopathic Physicians
and Surgeons, Los Angeles
R L SEARCY
L M BERGQUIST

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1 Gerrits, J C, Stolk, A, Verleur, H L. *Lancet* 1959, i, 470
2 Stern, J R, Mais, R F, Boggs, G D *Clin Chem* 1957, 3, 599
3 Talluto, K F, Benerito, R R, Singleton, W S *Analyt Chem* 1958, 30 1059
4 Zak, B, Jarkowski, T L, Williams, L A *Amer J clin Path* 1959, 31, 599
5 Wieme, R J *Clin chim acta*, 1959, 4, 317
6 Hakim, A A *ibid* p 484

THE SHORTAGE OF NURSES

SIR,—In his letter last week Mr Malkin has made some constructive suggestions about the present serious shortage of nurses This problem is closely associated with a grave and increasing shortage of hospital resident staff, and a great deal of the extra strain imposed on nurses is caused by unfilled, or inadequately filled, resident medical posts Many nurses are, in fact, carrying out duties which properly lie within the province of house-physicians and house-surgeons For this they get no recognition, and resentment at this state of affairs I am sure is increasing

Hospital practice conditions have changed tremendously since the inception of the National Health Service, and we must now realise that many resident medical posts in hospitals will not in future be filled Plans to continue our work must be made, possibly with the help of some form of technical assistant The Aftercare Sister, common at one time in orthopædic practice, is a very valuable person with much greater knowledge of the technicalities of orthopædic surgery than any newly qualified doctor She is, in fact, a recognised technical assistant, and handles alone without the presence of any doctor a form of clinic well known to orthopædic surgeons

The two problems—shortage of nurses and shortage of resident staff—should, I suggest, be considered together A central body consisting of representatives of the Ministry of Health, the hospitals, the British Medical Association, and the Royal College of Nursing, as proposed by Mr Malkin, seems ideally constituted for this purpose Within a short time of its formation the gravity of these two problems would be appreciated much more widely than at present The necessity for action to change our present system would be realised, and certain steps to improve the situation might soon become obvious The matter is certainly urgent

Northampton W R D MITCHELL

HUMAN RELATIONS IN OBSTETRIC PRACTICE

SIR,—As a psychiatrist I should like to express my complete agreement with Professor Morris (April 23)

When my wife was having her fourth child the obstetric surgeon said she should have it in hospital as she had a moderate macrocytic anæmia of pregnancy, but after I had seen the unit and sensed the impersonal and unsympathetic attitude of the sister-in-charge, who clearly resented my desire to see where my wife would have her baby, I preferred to risk a P P.H at home

Both friends and patients have many times told me of not only the absurd rituals they have had to endure but of the way their feelings have been disregarded and their opinions and wishes ignored.

The fault lies primarily, I think, with the obstetricians The majority of them are not sufficiently interested in the emotional feelings of their patients—if they were they would be as concerned as psychiatrists are at the present time to create a permissively relaxed and friendly atmosphere in their units, and this is clearly not the case In addition their treatment of women in gynæcological clinics is, so often, inhumanly impersonal and even occasionally brutal

The reproductive organs of women are of profound and deep psychological significance It is no accident that hysterectomy is a profoundly disturbing emotional experience to many women, an experience and trauma for which they should be prepared not only by explanation and reassurance but also by a friendly and understanding approach by all the staff of the unit.

After the birth of my first child my wife was seen by an eminent gynæcologist for some degree of prolapse His psychological approach was appallingly cold and indifferent As he is a teacher and an examiner there must be many obstetricians and gynæcologists who, having passed through his hands, are not very likely to have been taught to appreciate the emotional needs of their patients.

I believe much minor and some major psychological illness (particularly depression following hysterectomy) in women could be prevented if obstetricians and gynæcologists showed real understanding for their patients and tenderness in their approach. Ten minutes of explanation and reassurance in a unit where all the staff understand the principles of permissive psychotherapy in a non-authoritarian setting will prevent years of unhappiness and perhaps hours of a psychiatrist's time at a later date.

Far more emphasis on the emotional needs of patients and some understanding of the unconscious factors that lead to fears and anxieties about conception, childbirth, and gynæcological operations must be given to the doctors and nurses in training. Nevertheless I am afraid this will not entirely solve the problem, for there is no doubt that so much of the prevailing punitive attitude toward pregnant women is the projection on to the prospective mother of the unresolved conflicts concerning sex in the minds of the doctor and nurse, especially the senior hospital midwife. There is no doubt that many of these women are deeply jealous (often at an unconscious level) of their patients' ability to have children, and perhaps need to be made aware of their unconscious attitudes.

The Towers Hospital,
Humberstone, Leicester. H. B. KIDD.

LONG-ACTING SULPHONAMIDES AND PROTEIN-BINDING

SIR,—The paper by Mr. Newbould and Dr. Kilpatrick (April 23) is of considerable topical interest, since it reports a study of two new and widely used long-acting sulphonamides—sulphaphenylpyrazole ('Orisulf') and sulphamethoxypyridazine ('Lederkyn'). The compounds are compared with two well-established sulphonamides—sulphadimidine and sulphadiazine.

The methods used and the observations made are described in detail and with great clarity. The authors have with commendable scientific restraint refrained from drawing firm conclusions from their results. In view of this restraint, it seems particularly unfortunate that two statements appear in the paper which, as they stand, may mislead. I should therefore appreciate the opportunity of drawing attention to them.

(*a*) In the second paragraph of the preamble in reference to the two sulphonamides studied. "Though in-vitro these compounds had similar anti-bacterial activity to sulphadiazine, some of the results of clinical trials were disappointing (Harris et al. 1957, Prlina et al. 1958). Better results were claimed when larger doses were used (Walker and Hambukger 1957, Grieble and Jackson 1958, Jefferson 1958)."

(*b*) In the paragraph immediately preceding the summary on p. 891. "Toxic effects with these newer drugs have already been described (Holsinger et al. 1958, Lindsay et al. 1958, Schwartz and Norton 1958) and if larger doses have to be employed for therapeutic activity the patient may be exposed to a greater risk than that associated with sulphadimidine."

Eight references relative to these sentences are given. In none of these is sulphaphenylpyrazole mentioned.

A feature of sulphaphenylpyrazole is its remarkable freedom from toxic effects. A leading article[1] in the *British Medical Journal* recently said:

> "Pharmacological studies in man, confirming the prolonged action of this drug, were described by A. F. Essellier and his colleagues, by P. Rentchnick, who compared its behaviour with that of sulphamethoxypyridazine, and by D. Bachmann and his colleagues. All these authors also report good clinical results, perhaps the most enthusiastic paper being that by Essellier et al., since they claim success in the treatment of infections by bacteria most of which are said to have been sulphonamide-resistant, and in such conditions as chronic cholangitis and diverticulitis. One of the authors himself took 25 g. of sulphaphenylpyrazole daily for five days and experienced no ill effects—a bold demonstration of lack of toxicity."

Ciba Laboratories Limited,
Horsham, Sussex. A. K. PITTMAN
Director of Clinical Research.

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[1] *Brit. med. J.* 1959, ii, 482.

THE PERSONAL DOCTOR

SIR,—I trust Dr. Fox's article (April 2) will evoke the long, hard thinking it deserves and, I am sure, was intended to evoke, and I hope he will not be mistaken either for enemy to general practice or for a diehard conservative in need of a fresh demonstration by the sapient Canute. May I, as one lately retired from family and personal, if not general, practice, give some relevant evidence?

Beyond question the scope of general practice in the fields of medicine, surgery, and midwifery has contracted in the past 50 and perhaps especially in the past 20 years, most, no doubt, in the towns, but the country can hardly have escaped. Dr. James Mackenzie of Burnley, in the early years of the century, resecting loops of intestine and removing ovarian cysts in the intervals of unravelling the cardiac arrhythmias, could have thought me a sadly circumscribed specimen of general practitioner even 30 years ago, and if, in the last 10 years, he had chosen to say that I no longer deserved that proud title I could not have gainsaid him. There was no other name for me and my kind, but the number of things I no longer did for my patients increased, and to maintain birth-to-death continuous care became yearly harder. I am sure, too, that I was not alone in finding myself regrettably seldom the full, unquestioned doctor to the family I had so often been in earlier days. The disappearance of the nursing-home, so essential to continuous care in the type of practice prevailing in the neighbourhood, seems to prove that what happened to me happened also to my neighbours. In fact general practice and family practice have unquestionably been on the wane in the "residential area" of London about which alone I am qualified to speak. The term "personal doctor" would describe my professional occupation fairly accurately in the past five to ten years.

On the other hand I can and do vouch for it that in the field of "personal medicine" there has been no lack of work and that many patients, diverse in age, sex, occupation, and native land, do still find a use for a doctor "living over the shop", visiting them, when convenient or needful, in their homes, or listening to them, examining, advising, and medically ministering to them in a consulting-room furnished and equipped to his individual taste and expressing something of his personality. "I do like this room," they have said—as they might say of the consulting-rooms of many of my medical neighbours, and I am certain that, in a room they actively like, patients are more ready to give a history fully and without reservations, to ask the questions they ought to ask, and to listen to and accept advice, they are also—young ones especially—less likely to be frightened.

Sometimes I fear the personal doctor is doomed, as Dr. Ashworth so cheerfully and confidently prophesies, and that the citizens of the future will have a team or a clinic for his doctor. It could very easily happen. That blind, unreasoning power "the spirit of the age" perhaps still favours it, and if it is not to happen those who believe that something good would have perished must stand, individually and collectively, for their faith. If they want a little encouragement and Dr. Ashworth wants food for thought it is provided only 15 pages before his letter in your issue of April 23 where Dr. Norman Morris, writing of Human Relations in Obstetric Practice, quotes the opinions of some expectant mothers on some antenatal clinics Quite clearly they needed a personal doctor I hope—*how* I hope—that in this country it will never be impossible for them to get one

Crockham Hill,
Edenbridge, Kent LINDSEY W BATTEN

SIR,—I should like to support Dr Fox's contention that the general "comprehensive" practitioner, as such, no longer exists in this country I would also support his view that his successor is equally important His function must therefore be defined in clear terms May I take up some points raised in the correspondence following Dr Fox's article?

General comprehensive practice does exist and is not hypothetical as stated by Dr Hunt (April 9) An Australian friend described practice on a bush station where he was responsible for treating acute nephritis, trephining a skull, or doing a cæsarean section, and did so if necessary In other remote and isolated parts of the world many doctors are still doing quite complicated surgery and obstetrics as well as dealing with general medicine, psychiatry, and minor surgery This type of practice, properly termed general practice, was widely done in the nineteenth century in this country and has declined in this century to the present state of affairs where the general practitioner is no longer general in this original sense Medical schools have contributed to this decline, and the consequent decline in esteem, by emphasis on specialisation and horrific accounts of G P s' mistakes—e g , removal of both ovaries from young women because of simple cysts found at operation for appendicitis I do not know on what evidence Dr Hunt implies that general practice, even as defined by him, has been in existence for thousands of years The only evidence that he gives in the time of Hippocrates is to the contrary In modern times the barber-surgeon, physician, and apothecary were quite distinct, and I suspect that their functions were only brought together to create the general practitioner within the past two or three hundred years

It is as important for a specialist to have a general background as for a general practitioner Otherwise we shall have the worst kind of specialist Conversely the minute study of a small aspect of a special branch of medicine can deepen the understanding of medicine as a whole and of medical research, for those who are or will become general "personal" practitioners

In answer to Dr Ashworth (April 23), who thinks that a team should take over the family doctor's function, I would say that a personal doctor can still make use of nurses, receptionists, and laboratory aids (an extension of physical examination) as I do in my practice and at the same time preserve the individual personal relationship There is also no inherent reason why physical and psychiatric preventive medicine should not be carried out from the doctor's own surgery Most doctors of my acquaintance already undertake antenatal care and many fully immunise their patients

Having spent a year as a medical resident in a hospital in the United States I can confirm the tendency towards specialisation and towards the internist becoming the personal family doctor The latter process often leads to the internist having inadequate experience to remain expert in his specialty As an erstwhile medical registrar and present general practitioner and having had relatives needing close medical attention, my experience confirms the need for a personal doctor who will advise the patient on every aspect of health Whenever he feels competent, he should deal with the problem himself

Until the change in general practice is fully appreciated by the medical profession in this country, it is difficult to see how any positive approach to the definition of this essential aspect of medicine can be made Without this definition any great advance or regeneration is unlikely to take place This is not to say that there are no good general practitioners in this country But from most accounts regenerating forces are badly needed in some areas

Cambridge B B REISS

SIR,—I enjoyed Mr Malcolm Donaldson's letter of April 30, but if he will re-read mine he will see that I referred not to those who bellyached, but to those who bellyached about trivialia—an entirely different category

I should like also to explode this myth of the "overworked" doctor If a G P nowadays is overworked he is either unmethodical or has too large a list, or both

Crediton, Devon L N JACKSON

THE LATE DR JAMES BROWN A MEMORIAL LIBRARY

Dr D VEREL, of the Sheffield Region Cardiovascular Centre, City General Hospital, Sheffield, 5, writes

"Friends of the late Dr James Brown may like to know that his large collection of journals and cardiological reference books has been given to the department he founded to form a memorial library The majority of the journals have now been bound and housed in his old department where they constitute an invaluable source of reference A few issues of the cardiological journals are missing

"It may be that some colleague would be willing to present to this library the missing issues so that the collection can be completed The journals concerned are

"*Archives des Maladies du Cœur et des Vaisseaux*, three numbers missing between 1940 and 1956, *American Heart Journal*, three numbers missing between 1940 and 1956, *Circulation*, October, 1958, *British Heart Journal*, July, no 3, 1954

"Oddly enough, in most cases where a journal is missing there exists a duplicate journal of the wrong month"

Parliament

Payment of the Doctor

IN opening the debate on the Pilkington report in the House of Lords on April 27, Lord MORAN posed two questions why were the consultants, broadly speaking, content, and why were the general practitioners far from content? In his view the answer was that the principle of exceptional reward for exceptional merit was applied to one group but not to the other

He recalled that, when the National Health Service began, the system of merit awards was introduced despite the opposition of the Treasury, the British Medical Association, and the universities, and the indifference of the consultants themselves After ten years he believed that the position had completely altered The Royal Colleges had always been behind the awards, but now the council and representative meeting of the B M A were also unanimously in favour The Treasury had said, "There is nothing like this in the public service, but it seems to work, and we hope it will go on" Both the majority and the minority reports of the Royal Commission said, "These awards are the one imaginative feature in the whole of the Health Act" As chairman of the Awards Committee he naturally welcomed this change in the climate of opinion But though the Royal Commission had in principle approved of the awards system, they had, in Lord Moran's view, offered it disappointingly meagre practical support The addition of £500 to the A award and £250 to the B award did not make up for the change in the value of money over the past ten years A more serious criticism was that the number of awards, which in the past had increased as the number of consultants increased, had been frozen and fixed If the number of consultants continued to increase at the present rate, this would mean that in nine years time only 1 in 4 consultants, instead of as at present 1 in 3, would receive an award.

For the general practitioners, on the other hand, there had so far been no system of award, and to this lack Lord Moran firmly attributed their discontent. A general practitioner could add to his income only by increasing the number of his patients, and the present permitted maximum of 3500 was more than one man could look after. Many doctors with large lists had been hoping the Royal Commission would devise some means whereby a premium could be put on good work. The Royal Commission had responded by putting aside £500,000 and saying to the practitioners "You can have this if you can evolve a system". The problem of devising a scheme which would keep the general practitioner on his toes was not easy, but Lord Moran hoped that we should not be "fobbed off with the suggestion that instead of merit awards there should be responsibility awards, so as to avoid all the unpleasantness of deciding who is meritorious and who is not". Responsibility was synonymous with seniority. Those who were senior would no doubt welcome a financial bonus as a solace to the handicaps of advancing years, but it would not pay the community. To introduce these awards somebody was needed (perhaps, say, a Lord Waverley) who could arrive at the answer to a question by first principles and then, having come to his conclusion, refuse to budge an inch, no matter what the opposition. We did not want a Gallup poll of the sections of the profession to see what they were thinking at any moment. This would be one man's job. It would be a creative act, and, like all creative acts, it had got to happen in the brain of one man.

Lord Moran believed that the proposal for a review body was essential because for medicine the Government were a monopoly employer. They controlled the demand, the supply, and the pay of doctors. Was it any wonder that the profession was apprehensive of some arbitrary action on the part of the Government? And nothing that had happened in the last ten years had been very reassuring. Doctors had lost all faith in the Whitley machinery. We needed something absolutely new, and he implored the Minister to set up something on the lines of the proposed review body. Here was a golden opportunity to win the confidence and faith of the profession and to start a new era in the relations between the profession and the Government.

ALTERNATIVES TO THE COMMISSION'S RECOMMENDATIONS

Lord **Taylor** agreed that the proposed standing review committee was vitally important for future wage relations and structure. He regretted all the more that it had already been decided that the review committee were not to have access to the information which the Board of Inland Revenue had about the earnings of doctors and dentists and about the earnings of other professions. To collect the necessary information by repeated detailed questionnaires to busy professional people might well prove impossible.

Of some of the other recommendations he was more critical. For instance, he considered the proposal in the minority report for an average net annual income for the general practitioner of £2550 to be more in accordance with trend of pay in other professions than the Commission's figure of £2425. The first ten years of the N H S had clearly shown that the way in which a doctor is paid helped to determine the service he could give, and Lord Taylor's chief disappointment was that some of the Commission's recommendations would tend to work against the public interest. They described cash incentives to group practice as "somewhat excessive", and extra cash for rural doctors as "somewhat overdone". They doubted whether anyone was competent to set a top limit to the number of patients a doctor should have, yet the Ministry and the doctors between them had fixed in 1948 a limit of 4000 and, when the Danckwerts award came along, a limit of 3500. He agreed with Lord Moran that 3500 was still too high. Lord Taylor thought that when the Pilkington rates were introduced, despite the Commission's lack of directive, the opportunity should be taken to reduce the maximum permitted list to 3000.

The proposal for merit awards for general practitioners he dismissed, quite apart from its merits or demerits, as "out of this world". In his view nothing short of a two-day visit, living and working with a G P, would enable one to assess his real quality and merit, and there were 22,000 general practitioners from whom the fortunate 750 must be selected. Instead of merit awards he proposed a differential for age. A general practitioner's income (unlike a consultant's) started to fall when he reached the fifties, for general practice was one of the toughest physical jobs. He proposed giving the G P over fifty an extra £50 a year for each year between fifty-one and sixty, so that at sixty a general practitioner would get an extra £450 a year. The supplement might be linked with a minimum list of say 1000. He estimated that it would cost just over £1 million a year, or twice the Royal Commission's figure of £500,000 for the differential awards. It would put right a manifest wrong and would reward those who had borne the heat and the burden of the day and give them a chance to ease up a little when most of us eased up, without financial detriment to themselves and their junior partners.

Lord Taylor was grateful to the Royal Commission for providing the first proper statistical analysis of the awards given to consultants. It showed that every consultant had a more than even chance of getting an award before he retired. He was sure that all who received awards deserved them but he was uneasy about the 45% who never achieved merit. The effect on them was wholly bad. Could we be sure that among them were not many who deserved as well of their patients and the nation as the fortunate 55%? He believed that ultimately we should be driven to the view that the only honest and right thing to do for the future was to amalgamate the C merit awards with the general consultants' salaries. The invidious process of selecting at this comparatively low level of merit would end, to the great benefit of general hospital morale. Two-thirds of the awards were rightly divided among the 2000 teaching-hospital consultants, and he suggested that in future the B awards should be amalgamated with the salaries of teaching-hospital consultants and special regional-hospital-board units. The effect would be much the same as at present, but the invidious process of choosing and excluding would go. In the face of this, there was no real justification for the proposed A-plus awards, and it would be better to increase the number of A awards to, say, 450. Most of the consultants with A awards were part-time. Their private practices were doing well, thanks to the boom. These proposals would cost the nation no more than the Royal Commission's proposals; the Awards Committee would have to pick out only the top 450 men and women from the profession, instead of 2800, as at present. Those who were appointed to special posts would automatically get special recognition. But the secret division of staffs within hospitals into better-paid sheep and worse-paid goats would cease.

THE REVIEW BODY

The Earl of **Dundee**, speaking for the Government, gave some information about the new review body. It had been asked how the Government would interpret the recommendation that the members of this body should be appointed after "consultation" with the professions. On the one hand, it would not be constitutionally proper that the medical professions should have a formal right of veto of any member to be appointed; but the Government recognised that this body would be no use if its members were not acceptable to the professions. The comments of the professions would be invited on a provisional list of members, and their views would be fully taken into account. The Government would do their best to see that the medical profession would be satisfied with the membership. They were also ready to give an undertaking that any representations which the professions wished to make to the Review Body would be passed on to it by the Government, including any suggestions that for some particular reason a review earlier than the normal minimum period of three years might be desirable. The Government recognised that the medical profession attached special importance to being able to present their arguments to the review body orally, and were prepared to make a recommendation to the body that the professions should be given that opportunity if they wished to have it.

FURTHER DISCUSSION

Lord AMULREE, speaking as a part-time consultant, suggested that his colleagues, the whole-time consultants, laboured under some disadvantages, such as difficulty in getting allowances for travelling expenses to conferences, professional journals, and telephones He welcomed the substantial increases for young hospital doctors but he trusted that this time almost all the increase would not be absorbed by an increase in the charge for their keep He approved Lord Taylor's suggestion for a payment to elderly general practitioners He would like to see the N H S ensuring that the general practitioner had some leisure when he grew older

Lord COHEN OF BIRKENHEAD supported the system of merit awards—"wholly illogical in theory, but it works"—and did not want to see it modified according to Lord Taylor's suggestions But the present system had some anomalies, especially in universities, which he believed should be corrected For instance, preclinical medical staff were not eligible for awards He agreed that awards for general practitioners were desirable but doubted if they were practicable. Despite the unlikelihood of finding any other acceptable criteria than age and length of experience, he would like to see the proposal examined with a much larger sum in mind, so that not 1 general practitioner in 23 but perhaps 1 in 4 would receive an award. That might simplify the problem. But the least worthy reason for accepting the scheme was that it would be just another handful of silver for the kitty If a scheme for awards could not be devised he would like to see the money used for other purposes—such as incentives to single-handed general practitioners to take holidays, or help to general practitioners disabled in the course of their service. He hoped that the Royal Commission would have been the beginning—and that the review body would be the continuation—of a machinery which would prevent the disputes, the manifestoes, and ultimatums which had from time to time been displayed in public, and that the brilliant history of the National Health Service would not be scarred in the future, as it had been in the past, by unseemly wrangles

Baroness WOOTTON OF ABINGER said that the Royal Commission had collected for the first time evidence about relative professional earnings Her only regret was that they had not discussed its significance. Instead they had offered an ex-cathedra statement, with which she did not disagree, that doctors' earnings were too low According to the Willink Committee, there was at present an adequate supply of medical students in training A harsh and ruthless economist would have drawn the conclusion that the pay of doctors must therefore also be adequate But the Royal Commission, discarding thereby the whole of economic learning, blandly took the view that this meant that there was no relevance in the conditions of supply, and they dismissed them out of hand Nor did they substitute any alternative criterion, such as job analysis of the conditions of work of occupations that might compare with that of a doctor Having abandoned economics and having abandoned work comparability, the Royal Committee were left in a vacuum Thus the hierarchy of the profession as it stood would really be an expression of social conventions and of the values recognised and esteemed in our society We had these conventions, but we did not discuss them And the result was that we were gradually committing ourselves to an astonishing rigidity in the pattern of remuneration

GOVERNMENT REPLY

Lord ST OSWALD in ending the debate returned to the procedure of the review body The Government had undertaken to ensure that the profession was fully consulted on that body's membership They would also give a firm undertaking to pass on any recommendation made by the profession and to stress to the review body the importance attached by the profession to being able to present their case orally He was aware that doctors and dentists would prefer to be able, so to speak, to "press the button" themselves to set this machinery in action, though some doctors were not happy that any "monopoly employer" should be within reach of the button. But that was not among the recommendations of the Royal Commission, and it was not favoured by the Government as a unique privilege for the medical profession. The recommendations, as accepted, contained acceptance of the exclusion of doctors and dentists in the composition of this body Many doctors agreed that the position of professional delegates on the review body would be intolerable—that they would be blamed by their colleagues for every failure to act as a body as a whole or to act as the bulk of the profession. The Government were satisfied that it would not be practicable for the Inland Revenue to provide the review body with the information they required, and that body should be able to obtain it by other means List size would be a matter for discussion in detail as part of the consideration of the distribution of the pool Implementation of the report did not depend on the acceptance of merit awards for general practitioners Though he himself sympathised with the suggestion of extra payment for doctors over fifty he felt bound to point out that it would do away with the whole idea of merit, and he did not see how the £1½ million could be diverted to a completely different purpose.

Obituary

JULES FREUND

M.D Budapest.

Jules Freund died on April 22 in a hospital of the National Institutes of Health, Bethesda, Maryland, and with him died a pioneer in the field of immunology, whose name has become common coin among immunologists, by virtue of the technique he devised for enhancing antibody response.

He was born in 1890 in Budapest, where he qualified in medicine in 1913 After serving in the Austrian Army during the first World War he returned to Budapest as assistant professor of preventive medicine in 1917 In 1926 he went to the Henry Phipps Institute, Pennsylvania, and thereafter remained in the United States In 1932 Freund became assistant professor of pathology at Cornell, and in 1938 assistant director of the Bureau of Laboratories in New York.

During these years, in addition to more or less routine work on public-health laboratory methods, and serum and vaccine production, he studied the basic mechanisms of allergic reactions, especially in relation to antibody fixation in the body As a means of improving immunisation techniques he devised his well-known adjuvant method, by use of which he was able to produce the first fully authenticated experimental auto-immune disease—namely, testicular atrophy and sterility in guineapigs injected with their own testis material He also studied experimental allergic encephalomyelitis, which was found to occur when poliomyelitis vaccines containing brain tissue were used in conjunction with his adjuvant

When the Microbiological Institute of the National Institutes of Health changed its name and character, becoming the Institute of Allergy and Infectious Diseases, nobody was better suited than Freund to become chief of the laboratory of immunology Soon after taking up the appointment in 1957 he became aware that he had multiple myeloma, but he continued to work in the laboratory and with his colleagues, and to stimulate research throughout the National Institutes of Health until his death In October, 1959, he was honoured by receipt of an Albert Lasker Award of the American Public Health Association

Jules Freund was approachable, kindly, and always interested, with an infectious enthusiasm He and his wife Betsy, who was his great support, were much loved by many friends His widow and his son, Dr Thomas Freund, survive him

J H H

WILLIAM GRANT WAUGH

M A , M D Edin , F R C S E

Mr W Grant Waugh, who practised both in Durham and in London, died on April 25 in Alberta, Canada He was 73 years of age

T G L writes " Bill Waugh was a general practitioner, a G P surgeon, and a surgeon Courteous, gentle, friendly, and a natural aristocrat, he seemed a survival of some *ancient régime*, until a gleam of wit or a quiet remark revealed once more how up-to-date he had kept his mind His interests were not limited to the town where he practised, nor his intellect to his profession He held positions in a number of hospitals in Co Durham, and had a practice in Harley Street He was equally at home with his patients at both extremes He tackled a fracture, a uterine prolapse, a kidney stone, an empyema, or a peptic ulcer with equal enthusiasm He described an original plastic repair of a popliteal aneurysm, and a new biochemical approach to the osteoarthritic joint. He was a good judge of horseflesh (without being ' horsey '), and at one time would remark with pleasure that he owned half of one He did, in fact, combine his interests on one occasion His researches into the injection treatment of arthritis were first put to the test on a retired hunter, almost immobilised by arthritis After injecting the knees, he mounted at once and took her ' over the sticks ', thus staking his theories, his patient, and his own neck on the result He was widely read, both inside and outside medicine He contributed with perception, humanity, and facility to the clinical sections and correspondence columns of medical journals His last ' blast on the trumpet '—challenging, but melodious as ever—showed that there was no decline in his powers Was it fully appreciated, perhaps, that he could ' get something to bite upon ' and still keep his tongue in his cheek ?

" It is less than two years since Sunderland lost him, for he joined his son, Dr Ian Grant Waugh, to start a fresh life in Canada at seventy Our last news was of a new appointment in surgery at the local hospital Now the profession has lost him, and is fast losing his type He was one of the best of the Old Brigade, and we who follow will do well, if we do as well as he did "

Appointments

ADAMS, AILEEN K , M B Sheff , F.F.A. R.C.S , D.A part-time consultant in anæsthetics, Addenbrooke s Hospital, Cambridge
BARROW, JACK, M B Lond assistant, department of veneral diseases, St. Thomas' Hospital, London
EVANS, A J M.B Lond , D.A assistant, department of venereal diseases, St Thomas' Hospital, London
FORBES, R. Y , L.R C.P E , D P H depute M O H , Aberdeen
JOHNSTON, E N M , M B Cantab , M R C.P part-time consultant dermatologist, Nottingham and Mansfield hospital areas
LEIPER, JOHN, M.B E , M B Lpool, D.P H county M O , Cumberland
NEWBERRY, R G , M.B Lond , D.P H deputy M O H , school M O , and deputy port M O , Great Yarmouth
TREHARNE, ANNE E , M B Manc., D C.H school M O , Manchester
WILKINSON, R. H , M.D Cantab *consultant chemical pathologist*, United Oxford Hospitals

Birmingham Regional Hospital Board

BOURKE, J D , M B N U I , F F.A R C.S part-time consultant anæsthetist, Birmingham (Dudley Road) group of hospitals
DAVIS, F J , M.R.C.S., F F.A R C.S part-time consultant anæsthetist, Shrewsbury group of hospitals and Robert Jones and Agnes Hunt Orthopædic Hospital, Oswestry
LOWE, H G , M B Manc., F.R.C.S part-time consultant orthopædic surgeon Stafford group of hospitals
NOBLE, M J D , M.B Edin., F.R C.S.E , M.R C.O G part-time consultant obstetrician and gynæcologist, Birmingham (Dudley Road) group of hospitals

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Diary of the Week

MAY 8 TO 14

Sunday, 8th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W C.1
10 15 A.M Mr Maxwell Ellis Common Ear, Nose, and Throat Conditions

Monday, 9th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W 12
4 P.M Prof Feodor Lynen Co-enzyme A and Fat Metabolism.
WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St Mary's Hospital Medical School, W.2
5 P M Prof Albert Neuberger Digestion and Absorption of Protein in Normal Man and in Some Pathogenic Conditions (Almroth Wright lecture)

Tuesday, 10th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W C.2
5 45 P.M Prof G J Cunningham, Prof P C Koller, Dr R. J C. Harris Cell, Chromosome, and Virus Microscopy in Cancer Research.
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
5 30 P.M *Experimental Medicine & Therapeutics* Dr M Vogt, Dr P B. Bradley, Dr D M Leiberman Reserpine
8 P.M *Psychiatry* Dr T M Ling, Dr John Buckman Individual Psychotherapy with LSD Dr Joshua Bierer, Dr I Browne Treatment of Psychotic, Psychopathic and Emotionally Immature Patients with LSD and Group Psychotherapy in a Night Hospital Setting
ST MARY'S HOSPITAL MEDICAL SCHOOL
5 P.M Dr H A Davidson Male Infertility and Postcoital Examination.
INSTITUTE OF DERMATOLOGY, Lisle Street, W C.2
5 30 P.M Dr P E Bodkin Applied Physics
BIRMINGHAM MEDICAL INSTITUTE, 36, Harborne Road, Edgbaston, Birmingham.
8 P.M. *Psychiatry* Dr Leopold Stein Evolution of Human Language.
UNIVERSITY OF ST ANDREWS
5 P.M (Queen s College, Dundee) Dr Thue Poulson (Copenhagen) Aspects of the Treatment of Mitral Stenosis

Wednesday, 11th

UNIVERSITY OF LONDON
5 P.M (St Mary's Hospital Medical School) Prof G W Thorn Current Concepts—Glucocorticoids and Gluconeogenesis
5 30 P M (School of Pharmacy, 29, Brunswick Square, W C.1) Prof. H B Van Dyke (New York) Neurohypophyseal Hormones of Vertebrates
ROYAL SOCIETY OF MEDICINE
2.30 P M. *Proctology* Dr E R. Cullinan, Mr Tom Rowntree, Prof John Bruce, Mr R. W Raven Medical Management and Indications for Surgery in Diverticulosis and Diverticulitis
POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P M Dr K Weinbren Regeneration of the Liver
ROYAL FREE HOSPITAL, Gray's Inn Road, W C 1
5 P M. Dr J L Fahey (Bethesda) The Nature of Antibodies in Man.
INSTITUTE OF DERMATOLOGY
5 30 P.M Dr Henry Haber Eosinophilic Granulomas of the Skin.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W.3
5 P M Dr J C Batten Amyloid and the Lung
UNIVERSITY OF OXFORD
5 P.M (Radcliffe Infirmary) Prof R A McCance Development of Acid Base Control (Litchfield lecture.)
UNIVERSITY OF LEEDS
3 P.M (General Infirmary at Leeds) Sir Howard Florey Contributions of the Electron Microscope to the Understanding of Pathological Processes

Thursday, 12th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M Mr N C Tanner Technique and Late Results of Porto-Azygos Disconnection of Œsophageal Varices (Hunterian lecture)
ROYAL SOCIETY OF MEDICINE
5 P M *Ophthalmology* Mr F D McAuley, Mr Kenneth Newton, Mr John Watson Treatment of Tumours of the Eyelids
POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M Dr F Avery Jones Hæmatemesis and Melæna
INSTITUTE OF DERMATOLOGY
5.30 P.M Dr William Frain-Bell Benign Skin Conditions Requiring Radiotherapy
UNIVERSITY OF ST ANDREWS
5 P.M (Queen's College, Dundee) Dr J H Hutchison Cretinism and Juvenile Myxœdema

Friday, 13th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M Mr Lawrence Abel Cancer of the Rectum
INSTITUTE OF LARYNGOLOGY AND OTOLOGY
3.30 P M Mr J C Hogg Sinusitis
5 30 P M Dr G H Howells Significance of Orbital Swellings in Nasal Accessory Sinus Disease

Saturday, 14th

FELLOWSHIP OF POSTGRADUATE MEDICINE
10 A.M (St Stephen's Hospital, Fulham Road, S W 10) Prof C. E. Dent Metabolic Bone Disease Presenting as Vaguely Localised Pain (Inaugural lecture of a weekend course in rheumatic diseases)

Births, Marriages, and Deaths

DEATH

HOGG —On April 27, William James Hogg, M.D , of Forest Hill, Stonehaven, regional medical officer, Department of Health for Scotland

Notes and News

FOR THE YOUNG

Last Friday the King George's Jubilee Trust launched a silver jubilee appeal—the first national appeal since its foundation. As the Duke of Gloucester, the chairman of its council, has explained, this jubilee "will provide the occasion, and the means for reminding the adult community of their personal and individual responsibility for young people, and the young people themselves of their responsibility, as good citizens, to the community" The object of the Trust is "the advancement of the physical, mental, and spiritual welfare of the younger generation in the United Kingdom" It has spent more than £1 million in grants, but "the greatly increased number of young people and the practical effect of the decline in the value of money" have made its income of about £40,000 "wholly inadequate to meet the growing needs" A further £110,000 is wanted—particularly from contributions under covenant, from regular subscriptions, and from increased capital Particulars may be had from the appeal secretary at St. James's Palace, London, S W 1

The main object of the Trust is to help boys and girls who leave school at 15 Many of these lack opportunities to develop their good qualities, and these opportunities "must be brought within the reach of all, particularly those who are passing through the difficult time of transition from school to work"

> "Now, when increasing numbers of our boys and girls are entering employment, when public attention is focused on the shortcomings of at least some of them and when National Service is drawing to an end, is the opportune time to try imaginatively to arouse the interest of all young people in the qualities which make for good citizenship"

NUFFIELD TRAVELLING FELLOWSHIPS FOR GENERAL PRACTITIONERS

As part of its programme for the advancement of health, the Nuffield Foundation has generously given about £50,000, and, together with the College of General Practitioners, a scheme has been devised to enable general practitioners to undertake postgraduate study overseas during the next 4 years Twelve awards are for men or women from Great Britain, and one similar award will be made in rotation each year for a doctor from Australia, New Zealand, Canada, or South Africa The expenses of travelling and living will be met for the doctors (and their wives), and provision will be made for a locum for the general practitioners from this country

The first awards to men and women of the United Kingdom will be

Three *fellowships* (each for a period of 6 consecutive months) to enable general practitioners of outstanding ability, preferably between the ages of 35 and 45, to study overseas from July to December, 1961, in some subject of importance to general practice. The fellowship will cover for the fellow (and for his wife) tourist return travel by air, and other fares at tourist rates, together with an adequate subsistence allowance.

Three *assistantships* to enable doctors to gain experience as locum tenens in the practices of the fellowship holders The value of the assistantship award will be up to £750 for 6 months, in addition to travelling expenses

Applications for these awards must reach the Foundation by Oct. 31, 1960 The conditions of the fellowships and assistantships, and application forms, may be had from Mr L Farrer-Brown, The Nuffield Foundation, Nuffield Lodge, Regent's Park, London, N W 1

PROGNOSIS FOR ALCOHOLICS

What can a systematic course of 'Antabus' (disulfiram) treatment achieve, and can the prognosis in a given case of alcoholism be stated numerically? Berglin[1] goes some way towards answering both these questions From some 650 alcoholics given disulfiram treatment under the auspices of the Gothenburg municipal authorities and other bodies he selected 126 for an intensive statistical study made by a social worker who visited the patient's home with a questionary of 60 items A year after the completion of treatment, 31% of the 126 had achieved complete abstinence, and another 31% some improvement. The remaining 38% were no better and most of them later required institutional treatment. The answers to the 60 questions, by the alcoholic himself, or his immediate contacts, yielded information about his past and present and thus gave clues to his future. These clues are presented as so many points, good or bad, from which a numerical prognosis can be built up Minus points were earned by a history of drink before the age of 21 (25 points down) Other items on the minus side were a record of more than five bouts of drinking, the employment of some alternative beverage such as methylated spirits (19 points down), previous residence in some institution, a state of tension when sober, and a carefree attitude of psycho-infantile indifference to the problem of alcohol The importance attached to this last point was so great that it was down 40 Factors earning the alcoholic plus points make more cheerful reading If he had a record of sobriety during the first forty years of his life he could be marked 11 points up As many as 27 plus points could be allotted to the patient whose output of work during treatment was satisfactory Matrimony improved the prognosis by 13 points Berglin ends on a hopeful note by pointing out that all is not necessarily lost even when minus points tot up to a formidable total

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[1] Berglin, C G *Svenska Läkartidn* March 11, 1960

University of Glasgow

On April 30 the degree of M.D was conferred on I A. Porter

Royal College of Physicians of London

At a comitia of the college on April 28, with Sir Robert Platt, the president, in the chair the following were elected to the fellowship

W S Whimster, Nottingham J C J McEntee, London, L G Norman, London, W A Hawk, Canada P W Hutton, Uganda, Rustom Jal Vakil, India, Brian McArdle, London, Lord Taylor of Harlow, London, N F Coghill, London, Brigadier Mohammad Sarwar, Pakistan, Robert Mowbray, Durham, E B French Edinburgh, Sir Stanford Cade, London, A. A. G Lewis, London, Thomas Parkinson, Harpenden, Arthur Jordan, Sheffield, L L Rees, London, R B Thompson Newcastle upon Tyne, M E MacGregor, Warwick, D A R Pond, London, W E. Henley, New Zealand, B D R Wilson London, Major-General A. N T Meneces, R.A.M.C., Chester, C W M Whitty, Oxford, R. R. H Lovell, Australia, Lennox Eales, South Africa, C. H Edwards, London, J M. Jefferson, Birmingham, P F Borrie, London, J L. Frew, Australia, J P Shillingford, London, H L Ellis, Oxford, J D S Cameron, Edinburgh, A E Mourant, London, Harold Scarborough, Cardiff, D F. Cappell, Glasgow, R G Macfarlane, Oxford, Sir Clement Price Thomas, London, Arvid Wallgren, Stockholm

The following having satisfied the censors' board were elected to the membership

June P Arnold, M.D Lpool, Bryan Ashworth, M.B St. And., B W D Badley, M.B. Lond., Michael Barry, M.B. Cantab, Michael Brown, M.B. Lond., A A. Buchanan, M.B Lond, Devendra Nathan Chanmugam, M.B. Ceylon, M.B. Lond., R. D Cohen, M.B Cantab, J S Comaish, M.B Lpool, Joseph Connolly, M.B Lond, G H. Cooray, M.D Lond, A H Dimond, M.B. Cantab, C. G B Downie, M.B. Edin, Amal Kumar Dutta, M.B. Calcutta, A. T T Forrester M B Lond., Lionel Fry, M.B. Lond., Malay Bhushan Ghosh, M.B Calcutta, Binod Kumar Gupta, M.B. Lucknow, H M. Hodkinson, B.M Oxon, E E. Jones, M.B Lond., Abdel Salam Rafiq Kambawi, M.D Beirut, H J Liebeschuetz, B.M. Oxon., D R. London, B.M Oxon., J N MacCaig M.B. Manc., A. G Malleson, M.B Lond, Valerie J Marrian, M.B Edin. P D Marsden, M.B. Lond., N M C. Mayne, M.B Birm., G A. H Miller, B.M. Oxon., M G Miller, M.B Lond., R. O Moore, M.B N.Z., P M J O Brien, M.B. Lond., A. T Otaki, M.B. Lond., M S N Pathy, M.R C.P.E., O H D Portsmouth, M.B. Lond, A. I Rae, M.B Lond., Gordon Ross, M.B. Lond, Leo Stimmler, M.B. Lond., Fred Stratton M.D Manc., Mailoo Visuvaratnam, M.B Ceylon, J G Walker, M.B. Lond., J M Walker, M.B. Birm., R. E O Williams, M.D Lond, Poi Kwong Wong M.B Malaya, E. G Wooster, M.B Cantab

Licences to practise were conferred on the 178 candidates who have passed the final examination of the Conjoint Board

M. F A'Brook, A P Adams, E. J J Almeida J J R. Almeyda, Elisabeth M Appleby, Jean Arnold, Keith Arthur, N H Atkinson, Raphael Balcon, M A. Barnett, John Barrett, J M Barry, Ann A Barton Aref Sa d Bataineh, Brian Batten Pauline J Begley, H. E Berry, Delia A M Bickerton, John Bienenstock, Jean M Bird, R. C. Bland, Gerald Blandford, Barbara M Bonner-Morgan, P N Booth, W J Boyle, F E Bruckner, Jill A Bullimore, M J Campbell, P C. Cann, D McD Cardwell, A. A Carrasco, J A Carter, P G Cassell D N Challacombe, H M Clink, C. L. Colton, A R. Cook D E Cooksley, Dorothy J Cooper, T B Cork, Sheila A Corrin, Helena M J Cotter J E Crockett J C. Cummins, M F Cuthbert, D J W Darby, R. N Davies Jill Dean, P B Deverall, Sybil B Diggle, Ewa M Dragowska B R. Duncan E C. Emelife, A. W G English, J D Eustace, C. E Evans, P O Fasan R. E Faulkner, I T Field, H M Fisher T R. Fisher, D M Flanagan, Sally E. Flew, K. G E Frohnsdorf, Janet K Gambell, D H Georgelin, B E Gilliver Sharron H Gilmour, J C. Gingell P L. Girolami, Akude Gletsu, R. A Goldfinch, R. J Green, Susan R. Greenwood R. N Grunerberg, A D G Gunn, Pamela M Haigh, T R. Hailstone, J E. Hale J M Hawkins Alethea B Heal, Joseph Herbert, Rosemary E. Heron R. D Hill, B L. Houghton, R. H Hughes, G A Hunter, I M. James, M L. James, Cecily A Jenkins, B D Jones, H H G Jones, H D Kaufman, M J Kestle, Edvina M King, Thilla Krikler, D A H Langman, Alan Levine, D J Lightman, M J Lipton, J S P Lumley, Lawrence Lupin, Leonie M McEwen, M T MacMahon, I F Macrae, D J Martin, M H J Martin, R C Martin, C A S Mason, J R Massy, C D Matthews, Labhshanker Sukhlal Mehta, G M Michael, B S Michaels, J S Musgrove, Daphne M Newman, May Ning, E R Norton, V B Odunlami, M J Oliver, J D Parry, Catherine S Peckham, M. J Pemberton, Jean P Pettavel, Sally J Phillips, Dianne E Philp, Jeremy Pilcher, C J F Pool, David Prothero, A R Reece, G M Rees, Gunnar Reiman, D S Restall, Christine E Riley, I E W Robertson, R E Robinson, N C Roles, Wendy Roles, J B Sales, Naguib Abdelmalek Samaan, Elizabeth Shindler, A J Simmonds, G W Simonds, D H Smith, Joanna South, P E Spicer, Charmian R L Stephens, Patricia S Stephenson, Anne K Stewart, K E Tanner, W H Thomas, Ada A Thornton, C J Todes, D A Toms, L N Travis, K L K Trick, Irene J Tufft, William Ursell, J A S Vick, H Wagman, A E Walker, D E Walter, M M Watkins, W N D Watson, J L Wearn, P C Weaver, C L W Webb, Paul Wentworth, B W Whalley, N R Whiting, J N Whittaker, A R F Williams, Wendy E Williams, R A Wiseman, Bridget M. Wood, R B Woodd-Walker, M W G Wren, C H Young

The following diplomas and those mentioned in our issue of April 30 (p 988) were conferred jointly with the Royal College of Surgeons

D L O—Maung Maung Myint.
D O—P W E Downes
D T M & H—Johannes Olafsson

On Tuesday, June 21, at 5 P M, at the college, Pall Mall East, S W 1, Dr J G Scadding will give the Mitchell lecture He will speak on *Mycobacterium tuberculosis* in the ætiology of sarcoidosis

Royal College of Surgeons in Ireland

Faculty of Anæsthetists—This faculty has been instituted by the college and the following have been elected to the board

Dean, Dr T J Gilmartin, vice dean, Dr V O McCormick, Dr P Drury Byrne, Dr P Nagle, Dr S Kenny, Dr P Murray, Dr J A Woodcock, Dr R Davys, Dr J W Dundee, Dr S H Love, council representative, Mr D J Riordan, ex-officio, Mr T G Wilson, Mr S F Heatley

The president and council of the college will give Carmichael prizes of £150 and £100 for the best essays on the state of the medical profession in its different departments of physic, surgery, and pharmacy in Great Britain and Ireland, the state of the hospitals and schools of medicine, surgery, and pharmacy, and the state and mode of examination or of testing the qualifications of candidates of the different licensing colleges or corporations of medicine, surgery, and pharmacy Further particulars may be had from the registrar of the college, Dublin

British Association of Physical Medicine

Proposing the health of The Association at its annual dinner held at Apothecaries' Hall on April 29, Mr Derek Walker-Smith, the Minister of Health, spoke of the steadily growing interest in disorders of the locomotor system, dating from the first world war The medical progress made has been greatly helped by the Association with its specialised forum Now that people live longer they must not be passive survivors but must pursue positive health and active wellbeing

Dr Hugh Burt, the president, said that physicians practising physical medicine are having more and more cases referred to them for diagnosis, not merely for treatment, and those entering the specialty need a sound knowledge of medicine as a whole When the National Health Service started, there were 45 consultants in the subject but now there are 100, and a committee at present sitting may well propose that there should be more For a time orthopædic surgeons regarded practitioners of physical medicine with some suspicion, just as they themselves were once regarded with suspicion by general surgeons But bridging of the gulf " is of vital importance to the patients whom we both see ", and as evidence of it he welcomed the presence at this dinner, for the first time, of the president of the British Orthopædic Association, Mr H J Seddon

Squadron-leader C B Wynn Parry, in his amusing account of The Guests, also welcomed Mr Seddon, whom he described as " late instructor in surgery in the University of Michigan " Dr F Dudley Hart, responding, showed the wide range of interests suitable to a president of the Heberden Society The later phases of the evening had, he noted, induced a look of distaste on the face of James I, whose portrait hangs behind the high table, and whose *Counterblast to Tobacco* appeared 350 years before Doll and Bradford Hill

Royal Society of Medicine

Richard Kovacs prize (£50)—This prize is awarded triennially for work in physical medicine Applications should reach the hon secretary of the section of physical medicine, 1, Wimpole Street, London, W 1, by Sept 30

Royal Society

Prof Ragnar Granit, of Stockholm, has been elected a foreign member of this society for his researches on the physiology of vision and neurophysiology

Glasgow Medical Exhibition

The organisers of the London Medical Exhibition are to hold their annual regional medical show this year in Glasgow Mr Arthur Jacobs, P R F P S, will open it in the St Andrew's Hall, on Monday, May 23, at 2 45 P M It will remain open till May 27

First International Congress of Histochemistry and Cytochemistry

This congress will be held from Aug 28 to Sept 3 in Paris Further particulars may be had from the secretary-general, Dr R Wegmann, Institut d'Histochimie Médicale, 45, rue des Saints-Pères, Paris (6e), France

A weekend study course for those engaged in mental hospital therapeutic community work will be held at Burton Manor Residential College for Adult Education, Wirral, Cheshire, from July 1 to 3 The theme of the course will be Whither Psychiatry? The speakers will include Dr Russell Barton, Dr C R Lowe, Prof Thomas McKeown, Dr Richard Fox, Dr Pamela Mason, Dr Isaac Frost, and Dr James Brown Further particulars may be had from Dr Frost, Deva Hospital, Liverpool Road, Chester, or Dr George Egan, Liverpool Psychiatric Day Hospital, 10, Croxteth Road, Liverpool, 8

Mr R Y Calne, Dr Reginald Hall, and Dr I C Roddie have been awarded Harkness fellowships of the Commonwealth Fund tenable in the United States

Prof Ian Aird has left for Athens to help in the study of the projected school of postgraduate medicine at the Evangelismos Hospital. Later he is to visit Beirut as guest of the Middle East Conference of Surgeons

The annual dinner of the Regional Hospitals' Consultants and Specialists Association was held at the House of Commons on April 29 Mr Harold Dodd was in the chair, and the speakers included Lord Moran, Sir John Charles, Sir Stephen King-Hall, and Mr Robert Cooke, M P

The International Endoscopy and Cineradiology Society will hold its annual congress on Wednesday, May 25, at 2 15 P.M, at 1, Wimpole Street, London, W 1, under the presidency of Dr Frank Greenwood The speakers will include Mr H G Hanley Further particulars may be had from the hon secretary of the congress, Dr Brian Stanford, 54, Upper Montagu Street, W 1

The Older Worker and His Job—This short popular account of recent research on the skills and abilities of the elderly worker, and in particular of the studies described by Mr A T Welford in *Ageing and Human Skill* (see *Lancet*, 1958, ii, 1214), has been compiled by Hilary M Clay for the Department of Scientific and Industrial Research (Problems of Progress in Industry series no 7 H M Stationery Office, 1*s* 5*d* by post)

The poliomyelitis unit at Rush Green Hospital, Romford, Essex, have compiled a lively ward magazine, which has been typed by one of their members " by foot " Its title, *Puffin*, is typical of the courage and cheerfulness of this small company of frog-breathers and iron lung breathers They are appealing for £1000 to buy a motorvan to take some of them " out and about "

Copies of a new British standard for pressure steam sterilisers of small size (with independent steam supply) for unwrapped instruments and utensils (B S 3233 1960) may be had (4*s* each) from the British Standards Institution, Sales Branch, 2, Park Street, London, W 1

CORRIGENDA *Electronic Monitoring Apparatus for Coil Kidney*—In the article by Mr R Brennand and Dr N V Bunker (March 12, p 578) footnote 3 should have read Denison, A B, Spencer, M P *Rev sci Instrum* 1956, 27, 707

Infantile Structural Scoliosis—The last paragraph of Prof J I P James' letter of April 16 should have begun " Having seen well over 200 patients in ten years "

The Lancet · Saturday 14 May 1960

THE ACID-BASE METABOLISM

A NEW APPROACH

POUL ASTRUP
M D Copenhagen
K JORGENSEN
M.D Copenhagen
O SIGGAARD ANDERSEN
M D Copenhagen
K ENGEL
B Sc Copenhagen
From the Department of Clinical Chemistry, Rigshospitalet, Copenhagen

IN this paper we evaluate factors which characterise disturbances of the acid-base metabolism The importance of using chemical values, which are relevant from a clinical as well as a chemical point of view, is stressed and exemplified, and an analytical method is described for measuring the relevant chemical concentrations, using capillary blood, and available as a bedside procedure

Classification of Disturbances

The term *acidosis* should denote a pathological condition due to accumulation of acid or to loss of base These two possibilities may lead to the same clinical picture, as both tend to lower pH in the organism Similarly, alkalosis, or better *baseosis*, should mean a pathological condition due to accumulation of base or loss of acid

The terms " acid " and " base " are in this paper used for hydrogen-ion donor and acceptor, respectively, according to Brønsted (1923)

The use of these widely accepted definitions increases clarity (Devor 1953, Pretorius 1954, Relman 1954), especially because the acid-base metabolism can be dealt with independently of the cation metabolism Cations are neither acids nor bases and should consequently not be designated bases (e g , " total bases "), but cations

Of all acids and bases, carbonic acid is physiologically unique because of its high endogenous production, and because its concentration is regulated by respiration Disturbances primarily due to carbonic acid should therefore be clinically grouped separately Accordingly, each of the two conditions—acidosis and baseosis—can be further classified as either *respiratory* or *non-respiratory* The last group, often named " metabolic ", comprises all disturbances primarily due to fixed (non-volatile) acids and bases

Primary disturbance of the acid-base metabolism is usually compensated to some extent A respiratory disturbance is compensated by a renal mechanism, and a non-respiratory disturbance by a respiratory mechanism If, for instance, pH tends to fall because of an accumulation of some non-volatile acid, hyperventilation lowers the arterial pCO_2 (e g , Kussmaul's respiration) The actual state of a pathological condition can therefore be characterised also by its degree of compensation as *not compensated* (compensatory mechanism not working), *partially compensated* (pH not brought to normal value), *fully compensated* (pH normal), or *overcompensated*

The terms *acidæmia* and *alkalæmia* are used in some countries for conditions in which the pH of arterial blood is decreased or increased. These terms do not interfere with the classification given here

Estimations for Diagnosis

To indicate the severity of an acid-base disorder the following estimations have proved valuable in our experience.

Arterial blood pH depends on the relation between the respiratory and the non-respiratory components of the acid-base metabolism It thus reflects the combined influence of respiratory and non-respiratory disturbances

Any *deviation from the normal carbon-dioxide tension* (arterial pCO_2) reflects a *respiratory* acid-base disturbance, either primary or compensatory This accords with the general view

Any *deviation from the normal content of base* in blood reflects a *non-respiratory* acid-base disturbance, either primary or compensatory The base content should be expressed as *standard bicarbonate*, or as *base excess* or *base deficit* Standard bicarbonate is the concentration of bicarbonate in plasma, when whole blood has been equilibrated with carbon dioxide at a pCO_2 of 40 mm Hg at 38°C, and when the hæmoglobin is fully oxygenated (Jorgensen and Astrup 1957) Base excess (or base deficit) directly expresses the amount (in mEq) of strong base (or acid) added per litre blood, when the normal mean is arbitrarily fixed at zero Zero thus corresponds to the normal mean for standard bicarbonate (22 9 mEq per litre) When the term base excess (B E.) is used exclusively the *positive* values will express the excess of base, while the negative values will express the deficit of base (= excess of acid), and this makes for simplicity in practice

The normal 95% ranges of these values are arterial pH 7 35–7 42, arterial pCO_2 34–45 mm Hg, standard bicarbonate 21 3–24 8 mEq per litre, base excess −2 3 to +2 3 mEq per litre (Siggaard Andersen et al 1960)

When actual values found are considered the possible diagnoses are limited, and, together with clinical information, they usually lead readily to the exact diagnosis

Standard Bicarbonate and Base Excess

The word " standard " in standard bicarbonate should signify that the bicarbonate is measured under standard conditions in order to express only the non-respiratory side of the acid-base metabolism The standard conditions are a fixed pCO_2 and a fixed oxygenation of hæmoglobin, so that the influence of respiration on the base content of the blood is eliminated. We have chosen to measure with the hæmoglobin completely oxygenated and at a pCO_2 of 40 mm. Hg and at 38°C If, with these conditions fulfilled, the pH of blood is measured, the Henderson-Hasselbalch equation

$$\mathrm{pH} = 6\ 10 + \log \frac{\mathrm{HCO_3^-}}{\mathrm{pCO_2} \times 0\ 030}$$

will give the standard bicarbonate directly when the value of pH found and the value of pCO_2 (40 mm) chosen are inserted Full oxygenation of hæmoglobin is chosen for convenience, and also because it eliminates the small effect of accidental variations in oxygen saturation when venous samples are drawn. The determination of standard bicarbonate is very easy (Jorgensen and Astrup 1957)

Two other bicarbonate quantities, commonly used to indicate non-respiratory disturbances, are briefly mentioned for comparison *Total CO_2 of plasma* is the value determined by the manometric, volumetric, or titremetric techniques using plasma separated anaerobically from the cells The value varies,

TABLE I—PLASMA VALUES FOR TOTAL CO_2, CO_2-COMBINING POWER, AND STANDARD BICARBONATE, DETERMINED IN SAMPLES FROM THE SAME NORMAL BLOOD POOL, AT PCO_2 OF 20 AND 80 MM HG, WITH THE HÆMOGLOBIN COMPLETELY OXYGENATED AND COMPLETELY REDUCED

—	Hæmoglobin oxygenated		Hæmoglobin reduced	
	pCO_2 20 mm Hg	pCO_2 80 mm Hg	pCO_2 20 mm Hg	pCO_2 80 mm Hg
Total CO_2 (mM)	16 8	30 0	19 6	34 8
CO_2-combining power	19 0	26 7	22 0	31 4
Standard bicarbonate	21 2	21 2	21 2	21 2

Only the standard bicarbonate is independent of pCO_2 and oxygen saturation, thus showing its superiority in identifying non-respiratory disturbances

however, with the actual pCO_2 as well as with the oxygen saturation of the blood, and can therefore not be the ideal measure of non-respiratory disturbances This is illustrated in table I

CO_2-combining power of plasma is the total CO_2 of plasma, which is separated from the cells at the actual pCO_2 and then equilibrated at a pCO_2 of 40 mm Hg before measurement This value also varies with the actual pCO_2 and the oxygen saturation, though less than total CO_2 (table I)

Thus it seems evident that standard bicarbonate is the best *bicarbonate* value to measure when it is desired to eliminate the influence of the respiration and to determine the non-respiratory component only The effect of equilibrating whole blood seems to be approximately the same in vitro as in vivo (Shock and Hastings 1935)—i e, as if the respiratory function was standardised

The standard bicarbonate value has, like other bicarbonate values, the drawback that it does not show directly the amount, in mEq per litre blood, of fixed acid or base causing a change in the base content of a blood sample (This is because the carbon-dioxide/bicarbonate system is responsible for only about 75% of the buffer action of the blood against fixed acids and bases, when the pCO_2 is kept constant (see table II)) Therefore, to find the total deficit or excess for base per litre blood, the deviation of standard bicarbonate from the normal mean must be corrected, this can be approximately achieved by multiplying by 1 20 An exact correction requires knowledge of the buffer capacity of the blood—i e, the hæmoglobin concentration The advantage of using quantities which directly give the surplus amount of fixed acids or bases contained per litre blood is thus evident Here the use of change in buffer base or of base excess is helpful

Buffer base (Singer and Hastings 1942), which in all cases should be used in the form agreeing with the acid-base concept of Bronsted (1923), includes buffer anions other than bicarbonate, especially hæmoglobinate ions Thereby its value becomes independent of pCO_2, and a *change* in buffer base, in mEq per litre, directly expressed the amount of acid or base causing the change (table II) On the other hand, it represents a sum of factors of different buffer capacities Furthermore, *the buffer base value of a blood sample depends on its hæmoglobin and protein concentration* (table II) A patient with a low buffer-base value due to a low hæmoglobin concentration thus needs hæmoglobin and not bicarbonate

Concerning the quantity *base excess* (for definition see above), this gives directly, in mEq per litre blood, the surplus amount of fixed acid or base (table II) It is a quantity easily understood by those unfamiliar with clinical acid-base problems Further it allows the treatment of acid-base problems in a quantitative way So, from both a theoretical and a practical point of view, base excess is preferable to buffer base One argument against the use of base excess is that it does not give an ion-value for the base-concentration in blood If this is wanted the standard bicarbonate should be used, thus giving the bicarbonate concentration of plasma under standard conditions

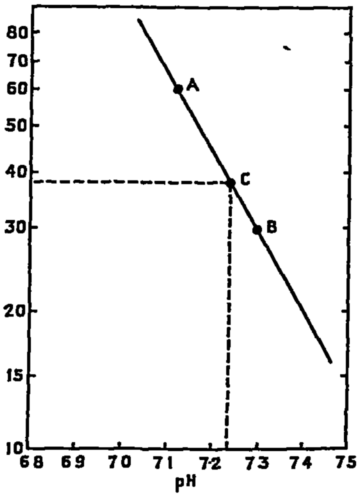

Fig 1—pH/log pCO_2 line for a blood sample

Point A indicates the measured pH value 7 12 after equilibration at pCO_2 = 60 mm Hg Similarly point B indicates pH 7 30 at pCO_2 = 30 mm Hg If, for instance, the actual pH of the anaerobically drawn blood had been measured to 7 24, the actual pCO would be read as 38 mm Hg (point C)

Total CO_2, CO_2-combining power, standard bicarbonate, buffer base, and base excess can be determined by the new microtechnique outlined below

Quantitative Treatment of Acid-base Disturbances

Respiratory Disturbances

Changes in the alveolar ventilation, leading to respiratory disturbances, are determined quantitatively by the pCO_2 of arterial blood, the value of which in general can be assumed to be identical with the value of pCO_2 of alveolar air

As the excreted amount of carbon dioxide per time unit is constant for an individual in a steady state, the

TABLE II—VALUES FOR BUFFER BASE, BASE EXCESS, AND STANDARD BICARBONATE, DETERMINED IN BLOOD SAMPLES WITH DIFFERENT CONCENTRATION OF HÆMOGLOBIN (15 AND 7 5 G PER 100 ML) AND WITH OR WITHOUT ADDITION OF STRONG ACID AND BASE (10 MEQ PER LITRE BLOOD)

—	Blood with 15 g hæmoglobin per 100 ml			Blood with 7 5 g hæmoglobin per 100 ml		
	No acid or base added	10 mEq strong acid added per litre blood	10 mEq strong base added per litre blood	No acid or base added	10 mEq strong acid added per litre blood	10 mEq strong base added per litre blood
Buffer base (mEq per litre blood)	46 2	36 2	56 2	43 4	33 4	53·4
Base excess (mEq per litre blood)	0	−10	+10	0	−10	+10
Standard bicarbonate (mEq per litre plasma)	22 9	15 9	30 7	22 4	15 4	31 0

The blood samples were obtained from a pool of normal blood (kept at 38 C, at pCO_2 = 40 mm Hg, and with the hæmoglobin completely oxygenated) The hæmoglobin concentration was altered by adding plasma product of the alveolar ventilation (A) and the pCO_2 of the arterial blood has a constant value (K) A × pCO_2 = K Accordingly, if the alveolar ventilation decreases, the pCO_2 must increase, and vice versa For instance, a decrease of A to half must double the pCO_2

In some cases additional laboratory measurements help in elucidating the cause of a respiratory disturbance Among these the measurement of the oxygen saturation or the oxygen tension (pO_2) of arterial blood is important Thus, a low oxygen saturation with a low pCO_2 is associated with completely different diseases to a low oxygen saturation with a high pCO_2

Non-respiratory Disturbances

When dealing with the *non-respiratory disturbances* knowledge of the total amount of excess acid or base in the organism can be of clinical importance The problems involved are rather complex, and for proper treatment knowledge of the distribution of acid and base in the different body-spaces and the rate of exchange between them is required The following approximations are helpful

The deficit or excess of base in *the extracellular body-space* can be estimated in mEq by multiplying the negative or positive value found for base excess, in mEq per litre blood, by 0 3 × the body-weight in kg, where the factor 0 3 is found experimentally (Mellemgaard and Astrup 1960) This amount corresponds directly to the amount of sodium bicarbonate or of ammonium chloride required to neutralise a non-respiratory disturbance in the *extracellular space*

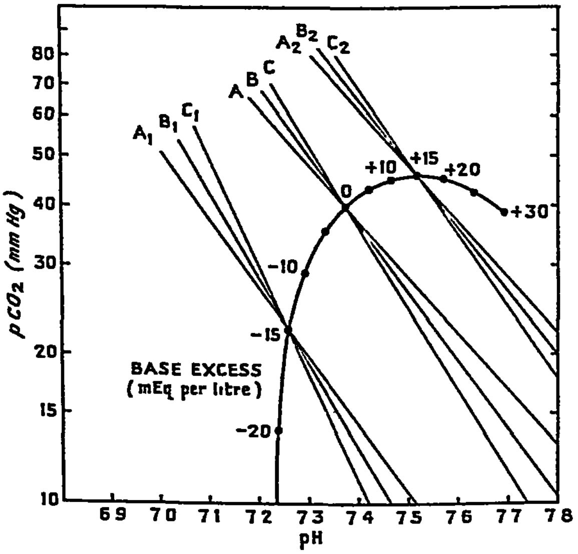

Fig 2—pH/log pCO_2 lines for blood samples with different hæmoglobin concentration and different content of base

A, B, and C represent samples of normal blood with a hæmoglobin concentration of 0, 10, and 20 g per 100 ml respectively A_1, B_1, and C_1 show the displacement after addition of fixed acid (15 mEq acetic acid per litre blood), and A_2, B_2, and C_2 after addition of base (15 mEq sodium carbonate per litre blood) The points of intersection of these lines form a curve (the base-excess curve) which indicates the amount of base excess (positive values) and base deficit (negative values) in any blood sample

For *the whole body*, the factor 0 7 should be used instead of 0 3 (Palmer and Van Slyke 1917)

In dealing with patients, however, the amount of excess or deficit of base in the whole body does not always seem to be directly proportional to the excess or deficit of base in the blood When, therefore, patients are to be treated with intravenous infusions of acid or base, it is advisable to estimate the dose necessary to normalise the base content of the extracellular space only, and then follow the effect of the treatment by frequent blood analyses and also by clinical observation, before new infusions are given Thus overtreatment is avoided (Mellemgaard and Astrup 1960)

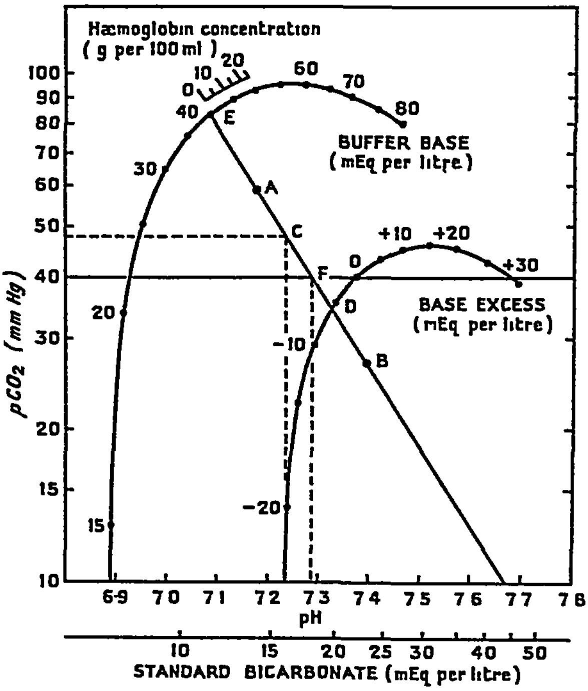

Fig 3—pH/log pCO_2 line for a blood sample, determined as described in fig 1

The point of intersection (D) with the base-excess curve indicates the amount of base excess to be −6 0 mEq per litre blood, while point E indicates the buffer base (= 40 mEq per litre) The standard bicarbonate (18 6 mEq per litre) can be derived from the pH value corresponding to pCO_2 = 40 mm Hg (F) The abscissa shows pH values and standard bicarbonate The total CO_2 of the plasma from the anaerobically drawn blood and the CO_2-combining power can be found from the figure (For this calculation see Siggaard Andersen and Engel 1960)

In treating the non-respiratory disturbances, it is important to estimate an abnormal loss of acid or base This is especially so when the loss is extrarenal—e g , in

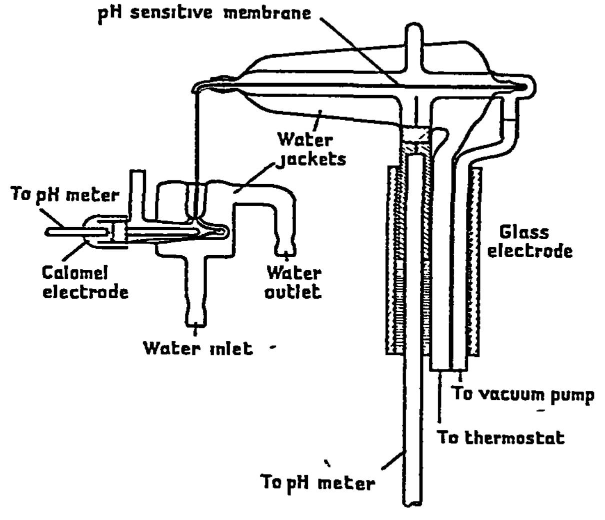

Fig 4—Capillary glass electrode for measuring blood-pH

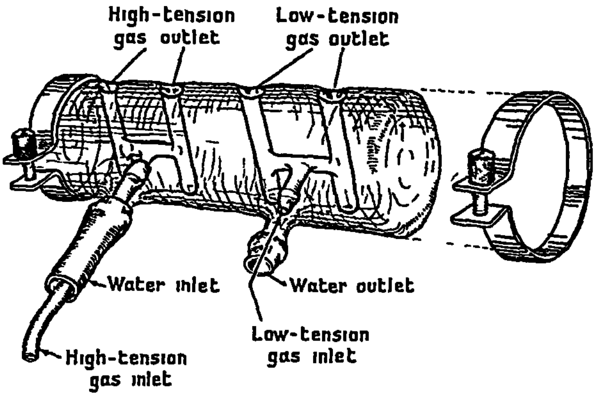

Fig 5—Chamber for simultaneous equilibration of microsamples in duplicate at two different carbon-dioxide tensions

pyloric stenosis and pancreatic fistula In such cases the lost amount of acid or base should be determined by titration together with the twenty-four-hour excretion of acid or base in urine (Jørgensen 1957)

Micromethod for Determining pH, pCO$_2$, Standard Bicarbonate, and Base Excess

When using macromethods for determining the above relevant values for characterising the acid-base status, arterial punctures are necessary This is a drawback when frequent analyses are needed—for instance at intervals of minutes in cases with rapid changes in the respiration (in anæsthesiology, treatment in a respirator, &c) A micromethod, using about 100 µl blood, was therefore developed (Siggaard Andersen et al 1960)

Principle

The theoretical background for the calculation of pCO$_2$, standard bicarbonate, and base excess is that graphs showing the relations between log pCO$_2$ and pH are approximately straight lines (shown experimentally by Brewin et al 1955 and Astrup 1956) The slope of the lines depends on the buffer capacity of the blood By equilibrating a blood sample at two known CO$_2$ tensions and measuring the pH values, the line for the sample is determined (fig 1) If the actual pH of the blood sample is known, then the actual pCO$_2$ can easily be found

When fixed acid is added to the blood, the line is displaced to the left When base is added, the line is displaced to the right Now a graph (fig 2) can be constructed expressing the displacement caused by any amount of acid or base, independent of the hæmoglobin concentration (Siggaard Andersen and Engel 1960)

The point of intersection between this curve and a found pH/log pCO$_2$ line for a blood sample thus indicates, in mEq, the base excess per litre blood

In the same diagram a curve can be constructed (Siggaard Andersen and Engel 1960) expressing the content of buffer base according to the definition of Singer and Hastings (1948) The curve is shown in the upper left corner in fig 3 By using this curve the amount of buffer base in blood can be found

Thus exact measurement of blood pH at the actual pCO$_2$ and at two known values for pCO$_2$ will allow the calculation of *all* relevant blood data concerning the acid-base status This is illustrated in fig 3

Equipment for Determination at Bedside

The equipment is described in detail elsewhere (*Siggaard Andersen, et al 1960*) *It consists of a pH*-meter, a circulating thermostat, a suction pump, a micro-electrode (fig 4) according to Sanz (1957), and a micro-equilibration chamber (fig 5) All these parts can be mounted on a portable table together with two small cylinders containing mixtures of oxygen and carbon dioxide

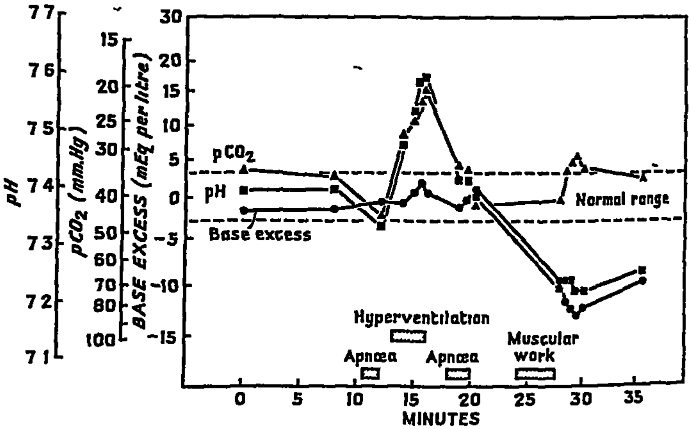

Fig 7—Case 2 values for pH, pCO$_2$, and base excess of blood from a normal person during a short period of maximal hyperventilation, apnœa as long as possible, and intensive muscular work.

The ordinate shows pH, pCO$_2$, and base excess, the abscissa time in minutes

Capillary blood is drawn from ear or finger For the actual pH about 20–25 µl is sucked directly into the capillary electrode (the principle of Sanz 1957) and the reading is made immediately, or it is sucked from blood drawn anaerobically into a heparinised capillary glass tube with sodium fluoride About 80–90 µl of blood from two capillary glass tubes is divided between two of the chambers in the equilibration apparatus This is then shaken mechanically (2600 r p m) and after three minutes the pH values in the two samples are measured successively By using these two values and the corresponding pCO$_2$ values (from the cylinders), the pH/log pCO$_2$ line is drawn and the pCO$_2$, standard bicarbonate, and base excess can be calculated (fig 3) The method is

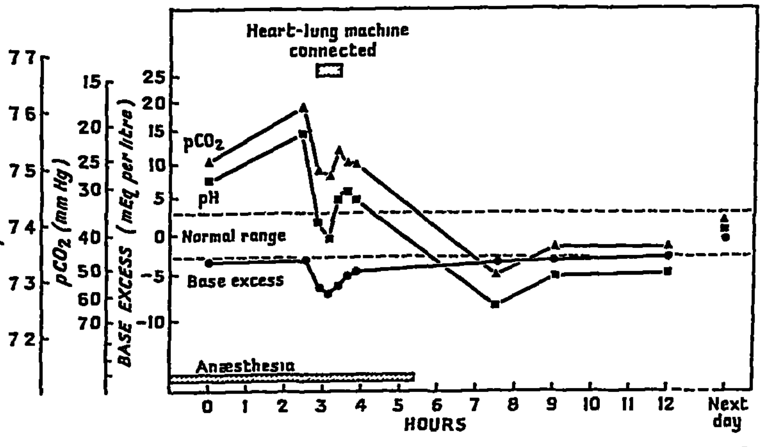

Fig 6—Case 1: values for pH, pCO$_2$, and base excess of blood from a patient operated on for a defect in the atrial septum

The ordinate shows pH, pCO$_2$, and base excess, the abscissa time in hours For further explanation see text highly accurate, as the three values can be found with an error of less than ±2%.

Illustrative Cases

The advantage of frequent registration of pH, pCO_2, and base excess by the method described here is illustrated in the following two cases. Figs. 6 and 7 show a convenient graphic system for these three quantities.

Case 1.—Fig. 6 shows blood values from a patient (female, 15 years old) operated on for a defect in the atrial septum. At the beginning of the operation the values for the non-respiratory component indicate a slight base deficit, possibly due to the postabsorptive phase. A manifest non-respiratory acidosis develops as soon as the blood of the patient is mixed with the rather acid donor blood from the heart-lung machine (approximately 4 litres with a base excess of −12 mEq. per litre, mainly due to lactic acid). The acid excess quickly decreases, partly by distribution between the different body compartments, and partly by oxidation of the lactic acid. The second day after the operation a normal value is reached.

The curve for the respiratory component (pCO_2) shows first the effect of overventilation during the anæsthesia. A slight rise in pCO_2 is seen when the heart-lung machine is responsible for the CO_2 excretion. When spontaneous respiration was established after the operation the pCO_2 was between 50 and 60 mm. Hg, reaching a normal value within a few hours.

The pH curve shows the resulting action of the respiratory and non-respiratory components on the hydrogen-ion concentration.

Case 2.—The pronounced deviations from normal acid-base values seen in a normal individual (male 26 years old) by maximal hyperventilation, periods of apnœa, and intensive muscular exercise of short duration are illustrated in fig. 7.

The rise in pCO_2 and the fall in pH during the two apnœa periods are moderate and obviously the fall in oxygen saturation (to about 80%, not measured accurately) is the limiting factor for the length of voluntary suspension of breath. During hyperventilation a fall in pCO_2 to about 20 mm. Hg was observed. The muscular exercise was followed by enormous hyperventilation, but the pCO_2 was now practically within normal limits. The explanation must be that the greatly increased CO_2 production is compensated by an equally increased CO_2 excretion by means of the hyperventilation.

Only small variations, within the normal limits, are seen during the pure respiratory changes. A possible cause of these small variations is displacement of base between the different body-spaces; this point deserves further investigation. During the muscular exercise a heavy non-respiratory acidosis develops, with a base excess of −12 mEq. per litre, indicating accumulation of large amounts of lactic acid.

Great fluctuation in the pH from 7.58 and 7.21, observed over a period of ten to fifteen minutes, was caused exclusively by a fall in pCO_2 and in base excess.

Summary

Disturbances in the acid-base metabolism have been classified according to the relation between blood values for pH, pCO_2, and an index of non-respiratory disturbances. This index should be either bicarbonate concentration measured under standard conditions as "standard bicarbonate" or else the surplus amount, as "base excess", of fixed acid or base in mEq. per litre blood. Knowledge of the value of base excess enables the total deficit or excess of base in the blood-volume and in the extracellular space to be calculated.

An accurate bedside method, using capillary blood, for determining all relevant blood values for the identification of disturbances in the acid-base metabolism, qualitatively and quantitatively, has been devised.

References at foot of next column

MEDICAL ASPECTS OF ROAD SAFETY *

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To drive safely requires the use of certain physical and mental qualities in reasonable degree. But these qualities can seldom be precisely defined and they cannot be quantified. Perhaps the nature and amount of the eyesight required for driving have been more fully established than those of other qualities, but even here the borderline between fitness and unfitness to drive is somewhat arbitrary.

In Great Britain in 1958 the police reported 992 road accidents in which a driver was ill or in which his physical defect was regarded as a contributory cause (Road Accidents 1958). This is a small proportion of the total number of accidents, but their prevention is of particular medical interest.

The clinical assessment of fitness to drive does not involve the development of yet another branch of Medicine. It is simply the application of clinical knowledge to the particular requirement of driving vehicles safely; and, as almost all doctors drive themselves, they are in the fortunate—and unusual—position of having practical experience of both sides of this question. Many adult patients are drivers who may seek advice on their fitness to drive during convalescence or in relation to chronic disease. This is especially important for professional drivers who may be responsible for the safety of many passengers.

A general guide for physicians on the assessment of fitness to drive has been published by the American Medical Association (1959) which has also produced a bright little booklet for patients, entitled "Are You Fit to Drive?" The British Medical Association (1954) and the World Health Organisation (1956) have also published helpful guides for physicians. These are not as well known as they should be.

In assessing the fitness of drivers it is usual to consider three types of vehicle: (1) the public-service vehicle in which seventy or more passengers may be carried, (2) the heavy commercial vehicle, and (3) the private car. The driver of public-service and commercial vehicles is a professional who generally drives for several hours a day, the private-car driver is usually an amateur whose driving may be for as little as half an hour a week or as much as eight hours a day—for example, some sales representatives. The risk of accident due to a medical condition in a driver increases with the time he spends driving. Hence, in assessing the fitness of patients to

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* The second Milroy lecture for 1960, delivered before the Royal College of Physicians of London on Feb. 4. The first lecture appeared last week.

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TABLE VI—LONDON TRANSPORT DRIVERS MEDICAL EXAMINATIONS AT CERTAIN AGES, 1959

—	Age											
	50		56		62		64		65–69		All ages	
	Examined	Found unfit	Examined	Found unfit	Examined	Found unfit	Examined	Found unfit	Examined	Found unfit	Examined	Found unfit
No of drivers	606	7 (1 1%)	515	15 (2 9%)	315	20 (6 3%)	195	9 (4 6%)	499	22 (4 4%)	2130	73 (3·4%)

drive, it is reasonable to take into account the number of hours a week for which they drive Higher standards of fitness are necessary for drivers of public-service vehicles, who have to obtain a medical certificate of fitness before their licence is issued (P S V Regulations 1934) Their medical examinations were described by Raffle (1959)

Road-service drivers in London Transport are medically examined at the ages of 50, 56, 62, 64, and annually thereafter (Norman 1958) The results in 2130 drivers examined in 1959 are shown in table VI Of the 73 who were found unfit, cardiovascular conditions were responsible in 51, visual defects in 7, arthritis in 2, diabetes in 2, and a variety of conditions in the remaining 11 Such drivers were recommended for other work As might be expected, a much higher proportion—23 6%—of drivers returning to work after illness were found unfit, temporarily or permanently Drivers need adequate convalescence after illness, both for their own safety and for that of other road users Sometimes their convalescence is too short because they want to return to full earning capacity

Loss of Consciousness While Driving

Assessment of fitness to drive is directed particularly at detecting conditions which may cause a sudden loss of consciousness These include

Simple faint (syncopal attack)
Cerebral anoxia (perhaps anæmia)
Falling asleep (and narcolepsy)
Postural hypotension
  (a) Ganglion-blocking agents
  (b) Splanchnic pooling
Psychogenic episode (hysteria)
Hæmorrhage into cerebral tumour
Aortic stenosis or regurgitation
Pulmonary embolism
Carotid-sinus syncope
Poisoning (e g , carbon monoxide)
Laryngeal vertigo (cough syncope)
Intestinal hæmorrhage
  (a) Massive
  (b) Slight recurrent, leading to syncope
Head injury (a) Subdural hæmatoma
Cerebrovascular accidents
Subarachnoid hæmorrhage
Epilepsy
  (a) Idiopathic
  (b) Space-filling lesion—e g , secondary to bronchial carcinoma
  (c) Triggered off by hypoglycæmia, alkalosis, or hypocalcæmia
Abnormal cardiac rhythm
  (a) Stokes-Adams attacks
  (b) Rarely auricular flutter or paroxysmal tachycardia
Myocardial infarction
Dissection of the aorta
Hypoglycæmia
  (a) Insulin
  (b) Spontaneous
  (c) Reactive

In the eleven years 1949–59 London Transport has employed an average of about 20,000 drivers, whose experience thus amounts to about 220,000 driver-years In this period there were 46 cases in which a driver lost consciousness suddenly while driving Lest this figure be thought rather high, I should point out that the average passenger would have had to ride for about an hour a day for nearly thirty-five thousand years before being involved in such an accident A summary of these cases is given in table VII The ages of the drivers ranged from 36 to 63, with no particular prevalence in any one age-group, only 5 were over 60 The following case illustrates the type of investigations made after an incident of this kind

A man aged 47 was driving a bus one evening when he lost consciousness suddenly The bus is thought to have been out of control for about 60 yards, and, swerving to the offside of the road, it demolished about 20 yards of low wall Nobody was injured When the driver recovered consciousness a few minutes later, he remembered nothing of the incident He was under treatment for a duodenal ulcer, and for fear of vomiting he had not eaten any food that day In hospital it was thought that dehydration, alkalosis, and hypoglycæmia together had triggered off an epileptic attack Other work with no driving was found for him

Hypertension

Little is known of the relation, if any, between accident-rates and blood-pressure Blood-pressure measurements are therefore directed towards prediction of such events as cerebrovascular accidents, coronary infarction, dissection of the aorta, Stokes-Adams attacks, vertigo, and fainting Any of these conditions, occuring without sufficient warning may result in a serious accident Though such conditions are not directly related to the blood-pressure there is a level of pressure at which the risk of cerebrovascular accidents is too high to accept The difficulty is to define this critical level, especially where blood-pressure readings are casual ones taken in the consulting-room Moreover, emotional disturbances while driving may raise the blood-pressure

In 1958, a man aged 58 was driving a bus when he suddenly lost consciousness and the bus collided with a trolleybus standard There was no previous history of illness and the sickness record showed only occasional minor absences He died without regaining consciousness and necropsy revealed a large cerebral hæmorrhage with evidence of gross hypertension He had attended the medical department only for routine eye-sight tests, and his blood-pressure had not been recorded Under present arrangements his hypertension would have been found at routine age examinations

TABLE VII—DIAGNOSIS IN CASES WHERE DRIVERS LOST CONSCIOUSNESS, 1949–59

Diagnosis	No of cases	No of cases in which collision or other accident resulted
Coronary infarction	14	3
Laryngeal vertigo	2	2
Whooping-cough	1	1
Lobar pneumonia	1	
Hypertensive encephalopathy	1	1
Probable epilepsy	8	8
Reflex hypotension from muscular cramp	1	1
Simple faint (vasovagal syncope)	5	5
Subarachnoid hæmorrhage	1	1
Cerebral hæmorrhage	1	1
Reactive hypoglycæmia	1	1
Onset of febrile illness (" influenza ")	1	1
Convalescent after illness (influenza ")	1	
Unknown	8	1
Total	46	26

In two other cases in which men lost consciousness while driving, the only abnormality found was hypertension, the blood-pressures being 255/140 and 280/130 mm. Hg respectively.

The World Health Organisation (1956) recommends that in essential hypertension, where the systolic pressure is persistently above 200 mm. Hg or the diastolic pressure persistently above 100 mm. Hg, driving of a heavy motor vehicle should not be permitted. This view may be too rigid. The American Medical Association guide says that hypertension in itself does not interfere with the safe operation of a motor vehicle, but that "complications arising from hypertension, i.e., damage to brain, eyes, heart or kidneys, may well prove to be so disabling". The A.M.A. also recommends that when "the complications of hypertension are limited to the optic fundi, the degree of impairment of driving ability should be evaluated solely on the basis of loss of vision". However, ophthalmoscopy is essential for the assessment of the significance of hypertension.

In assessing the fitness of public-service drivers, a level of hypertension has been chosen which is regarded as borderline; ten other factors are then taken into consideration. The borderline case is that of a man aged 55, with a systolic pressure of 210 mm. Hg or a diastolic pressure of 105 mm. Hg. Below these levels he is considered fit to continue driving, but if he is near either level he is again examined in six or twelve months. The driver rests for at least fifteen minutes before readings are taken, and two measurements at a week's interval may be made. Corrections for arm circumference are not normally applied and measurements are usually made on one arm only. To avoid creating anxiety, measurements are generally not repeated more than once during any one examination.

The ten factors taken into consideration are:

1. *Age.*—As the risk of cerebrovascular accidents increases with advancing age, the borderline level becomes 200 mm. Hg systolic or 100 mm. diastolic at the age of 65.
2. A *family history* devoid of cerebrovascular and cardiovascular troubles improves the prognosis.
3. *Symptoms.*—Mild occipital headaches are not regarded as significant. A history of angina pectoris, vertigo, 'stroke', transient loss of cerebral function, or any residual neurological abnormality on examination, is a bar to driving.
4. *Fundus oculi.*—Retinopathy of grades III and IV would generally bar from driving.
5. *Albuminuria* of more than a trace worsens the prognosis and the driver is certified unfit.
6. *Glycosuria*, if present, does not adversely affect hypertension and is dealt with as given under Diabetes (see below).
7. *Overweight*, if more than 20% above the life-assurance standards (Conduct of Life Assurance Examinations 1949), is an adverse factor.
8. *Organic arrhythmias*, if present, generally bar from driving.
9. *Electrocardiogram.*—Gross abnormalities bar from driving.
10. *Chest radiograph.*—Cardiac enlargement of more than minor degrees bars from driving.

Broadly similar recommendations for public-service drivers were made by the Royal Australian College of Physicians (1959). The standards for public-service drivers are more strict than those which should probably be applied in advising private-car drivers. For the latter, hypertension, unless extreme or accompanied by complications, is not usually considered a bar to driving.

During 1959, 39 London Transport drivers were found unfit because of hypertension. Blood-pressure readings ranged from 180/120 to 260/150, and the majority also showed evidence of hypertensive vascular disease. Only 1 of these drivers was over the age of 65—presumably because most hypertensives had been eliminated at previous examinations.

Ischæmic Heart-disease

About a third of cases of loss of consciousness when driving are due to coronary infarction. In 1949–59 among some 20,000 London Transport drivers 14 cases occurred (table VIII).

That there were only 14 cases in 220,000 driver-years of exposure emphasises the small size of the risk, but in an undertaking as large as London Transport this amounts to about one case in every ten months. Of the 12 cases in which the vehicle was moving, there were 5 where the driver did not seem to have enough warning to stop the vehicle, and 3 of those resulted in accidents. Morris et al. (1952 and 1957) and Morris (1958), in their study of doctors, showed that the risk of a second coronary episode may be ten times as high as the risk of a first. Hence a diagnosis of myocardial infarction excludes a man from driving public-service vehicles. Unequivocal electrocardiographic changes indicating previous myocardial infarction also exclude him, whether he has symptoms or not. The Royal Australian College of Physicians (1959) and the American Medical Association (1959) agree with these views.

TABLE VIII—DRIVERS EXPERIENCING LOSS OF CONSCIOUSNESS DUE TO CORONARY INFARCTION WHILE DRIVING, 1949–59

Case no.	Any collision or damage?	Did driver have sufficient warning to stop the vehicle?
1	No	Vehicle stationary
2	No	No
3	No	Yes
4	No	Yes
5	Yes	No
6	Yes	No
7	No	Yes
8	No	No
9	Yes	No
10	No	Yes
11	No	Yes
12	No	Yes
13	No	Yes
14	No	Vehicle stationary

A diagnosis of angina pectoris should exclude a man from driving public-service vehicles. The risk of sudden loss of consciousness while driving is probably as great in such a person as in one who has recovered from myocardial infarction.

Electrocardiograms are not taken for London Transport drivers as a routine, but only when clinically indicated.

Apart from variation in the interpretation of electrocardiograms (Davies 1958) there is the practical difficulty that perhaps as many as 20% of men over 50 show minor abnormalities. Changes after exercise, of a degree usually held to indicate coronary heart-disease, were found by Acheson (1957) in 15% of fit symptomless R.A.F. men aged 20–40. Whether these changes are an indication of future coronary disease will not be known until these men have been observed for a further long period. To exclude all drivers with minor electrocardiographic abnormalities would be unfair in most cases and would seriously deplete the numbers of drivers available to the undertaking.

To take an electrocardiogram when a driver is first employed would probably be helpful, both to serve as a baseline for later investigation and to establish the existence of unimportant congenital variations such as left bundle-branch block.

By various examinations one can select a small proportion of the population who are symptomless but who have hypertension, a family history of coronary heart-disease, and a high blood-cholesterol (especially the β-lipoprotein fractions), and are overweight. At present it is not thought justifiable to remove such men from driving, but if further research reveals a small proportion of drivers who carry a very high risk this problem will have to be reconsidered What probably matters most is whether the driver is genetically equipped to deal with cholesterol, and this cannot yet be ascertained

It is generally held that people who have made a good recovery from coronary infarction, or whose attacks of angina are mild and infrequent may continue to drive private cars

Epilepsy

The applicant for a licence must answer the question " Do you suffer from epilepsy, or from sudden attacks of disabling giddiness or fainting ? " A patient who is under treatment and has had no fits for two years might well answer " No " to this question, which could usefully be reworded, " Have you ever suffered from epilepsy ? " Driving licences are now issued for three years, and the holder is not under an obligation to inform the authorities if he develops epilepsy during that period There is no legal ruling which governs the issue of driving licences to epileptics in the United Kingdom

Until about 1948 it was generally held that a person who has at any time suffered from fits should be refused a driving licence (Symonds 1948) The World Health Organisation (1956) recommended that applicants who gave a history of any form of epilepsy should not be permitted to drive The present tendency is to relax this ruling, but only in respect of private-car drivers In Britain it is generally held that an epileptic who remains under observation or treatment, and who has been free from attacks for at least three years, may drive a private car, though not public-service or commercial vehicles The American Medical Association (1959) says that epileptic patients who are not receiving medicaments and who have been free from seizures for at least two years may be allowed to drive private cars but not commercial or passenger vehicles The Association recommend that such patients should be advised not to take any alcoholic drinks for at least twenty-four hours before driving, and not to drive for more than six hours in any day driving at night may be dangerous because photic stimuli from opposing headlights may precipitate a seizure, and emotional stress should be minimised by avoiding driving in peak hours These restrictions probably reflect uncertainty about the safety of such patients as drivers

In the U S A the present practice varies from State to State

In eighteen States licences are granted to epileptics on the basis of medical control of seizures, in others an interval of one to three years' freedom is required (Dewey 1955) The State of New York, among others, has laid down a detailed procedure for judging applications (Hilleboe 1959) In Massachusetts (Bonzagni 1954) an applicant who has had epilepsy must present a statement from an approved neurologist, saying that he has been treated, that he has had no seizures for at least eighteen months, and that the physician recommends the issue of a licence From 1948 to 1954, 512 epileptics applied for licences and 392 were issued on a probationary basis requiring the submission of periodic certificates

In California, where the procedure is based on a report by Glaser and Irons (1946), epilepsy is a notifiable disease, being defined as " any condition which brings about momentary lapses of consciousness and which may become chronic " All hospitals and many doctors comply with the requirement to notify epilepsy, and about 4000 notifications are received annually In 1957, licences were withdrawn from 936 drivers because of epilepsy A further 524 patients who were under treatment at the time of notification were allowed to retain their licences but told to submit medical reports every three to six months The policy is to require three years' freedom from any lapses of consciousness before a driving licence is restored, but in a cooperative person who has had only a few attacks this period may be reduced to two years This procedure has been found to work well (James 1958) An obvious difficulty is that compulsory notification may lead to concealment, but California appears to have overcome this

In 3 London Transport employees an epileptic fit (not while driving) was the first indication that the patient had a carcinoma of the bronchus As secondaries in the brain may occur in 15% of cases of lung cancer (Simpson 1929), bus drivers who resume work after treatment of this disease are not allowed to continue driving

Diabetes Mellitus

Patients whose diabetes is controlled by diet alone are considered fit to drive any type of motor vehicle There is general agreement that those who require insulin, even in small doses, should not drive public-service or heavy commercial vehicles

Copplestone (1959), in a survey of 56 diabetic drivers who were taking insulin, reported 3 accidents within five years—all in people who said they were not liable to insulin reactions A controlled study of accident-rates was not possible in this survey Brandaleone and Friedman (1953) found no excess of accidents among 13 bus operators who were diabetics, but these patients were not receiving insulin

No comparative studies of accident-rates in diabetic drivers have been made, and there is in any case so much variation between individuals that no safe rule can be laid down In general, a diabetic receiving insulin is fit to drive a private car if his hypoglycæmic attacks are mild and of slow onset Rarely, the nature of the attacks changes, and if a patient has sudden or rapid loss of consciousness he should be advised not to drive The Law has no sympathy for diabetics The Lord Chief Justice in Armstrong *v* Clark (1957) stated that insulin is a drug within the meaning of the Road Traffic Act, 1930

A man of 51 was driving a coach for a provincial company when there was a collision with a van He was unable to stand without support, a police officer correctly diagnosed hypoglycæmia and administered sugar This driver had missed his usual meal at 2 P M He pleaded guilty to driving under the influence of a drug and was fined, and disqualified for twelve months He had been treated with insulin for only nine months

In the early months of insulin treatment, fluctuations and adjustments are to be expected, and during the first year's treatment special care should be given to drivers and the importance and treatment of hypoglycæmic attacks explained to them Every insulin-treated patient who drives should be made to experience a fairly severe insulin reaction, for otherwise the mild symptoms usually induced at the outset of treatment may give him the impression that insulin reactions are unimportant for him In these cases the risks arise entirely from treatment

Complications of diabetes may render a patient unfit to drive, but such complications are considered on their own merits Thus ocular complications are considered in relation to any defect of vision they may produce *Renal glycosuria* does not affect driving

Reactive or functional hypoglycæmia may be of considerable importance

When there is a quick rise in blood-sugar followed by a rapid fall, the level may occasionally go down to 50 mg, or less, per 100 ml, with actual loss of consciousness An example in which the patient had an epileptiform attack while in charge of his car is reported by Hay (1958), who thinks that functional hypoglycæmia probably accounts for some road accidents Disturbances in behaviour resulting from lesser degrees of hypoglycæmia may be associated with some accidents, but nothing is known about this

Patients who give evidence of reactive hypoglycæmia should avoid meals consisting almost entirely of carbohydrates The common present-day habit of going to work fasting, or after a breakfast of toast, marmalade, and sweet tea, may accentuate any tendency to this condition People who undertake a long drive should have a well-balanced meal beforehand Hypoglycæmia may be the trigger for an epileptiform attack, and, in any event, people whose consciousness is so labile that they lose it simply by missing breakfast, or through eating a carbohydrate breakfast, should not drive public-service or heavy commercial vehicles If they appear to understand the condition and act reasonably, they may drive private cars

Similarly, people whose diabetes is controlled by oral hypoglycæmic agents, such as tolbutamide may usually be allowed to drive private cars provided they are aware of the possibility of hypoglycæmia At present it is felt that they should not drive public-service or heavy commercial vehicles, but this view may be modified with experience

Visual Requirements for Driving

The driver is continually receiving auditory and tactile as well as ocular information, but the ocular information is the most important. The data supplied by a defective ocular apparatus may be incorrect, blurred, incomplete, or delayed

Several studies have been made in the United States of the relation between visual acuity and accidents

Lauer et al (1939), using two different tests of visual acuity, found that higher acuity was associated with fewer accidents Brody (1941) found that 4 out of 26 accident-repeaters had an acuity lower than 20/30 in the better eye and 20 50 in the worse eye A comparison of a group of accident-repeaters with a group of accident-free drivers undertaken by the New York Centre for Safety Education indicated that drivers with poor visual acuity are more likely to be involved in accidents than drivers with good acuity (Smeed 1953) Fletcher (1942) found that the proportions of drivers who failed tests of visual acuity were 1% for drivers with good accident records and 5% for drivers with poor records

These investigations confirm that drivers with poor visual acuity tend to have more accidents than drivers with good acuity, but the point at which impairment of acuity becomes a cause of accidents is unknown (Perhaps there is no such point, even the slightest impairment increasing accident liability to some extent) In further studies attention should be paid to different conditions of illumination, which, as Davey (1956) has shown, considerably affect visual acuity This is illustrated in table IX.

14 drivers aged 50–65 were tested on Snellen's types indoors, with an illumination of 35 lumens on the test chart and immediately afterwards out of doors in June and July, 1958, in conditions varying from cloudy to bright sunshine (table IX) In the stronger light outdoors, 1 of the 28 eyes improved in visual acuity from 6 60 to 6/12 and 10 improved at least three lines on the test chart, all 28 improved at least one line Visual efficiency increases with higher illumination, but the improvement in acuity shown by these men is largely due to reduction in the size of the pupil No quantitative relation is to be expected, for age, pigmentation, refractive error, and emotional state all affect the reaction of the pupil to changes in retinal illumination

TABLE IX—RESULTS OF VISUAL ACUITY (SNELLEN) TESTS ON 14 DRIVERS UNDER DIFFERENT CONDITIONS OF ILLUMINATION

Indoor reading (35 lumens on chart)	No of eyes	Outdoor reading		
6 60	5	6 24 (2)	6 18 (2)	6 12 (1)
6 36	7	6 18 (3)	6 12 (3)	6 9 (1)
6 24	2	6 12 (2)		
6 18	3	6 9 (1)	6 6 (2)	
6 12	5	6 9 (2)	6 5 (3)	
6 9	3	6 6 (1)	6 5 (2)	
6 6	3	6 5 (3)		

At night a driver s visual acuity may be worsened by this intrinsic factor as well as by reduced visibility

Smeed (1953) studied the changes in adult pedestrian casualties which occurred when summertime was introduced and removed He found that in the hours that change from light to dark the number of casualties was approximately doubled, while in those that change from dark to light the number was halved There appeared to be no changes in traffic density which could explain these findings

One main problem at night is that of dazzle, and Savin et al (1957) point out that " dark glasses can help against dazzle, but at the expense of lowering general visibility " It cannot be too strongly emphasised that any coloured glass in front of the eyes—spectacles, a tinted windscreen, or an anti-dazzle visor—is an obstruction to the driver's vision and should not be used at night Under simulated night-driving conditions, with glare, Miles (1955) measured the effect of tinted glass on the visual acuity of subjects having normal daylight vision Tinted glass, of all colours, always reduced visual acuity, the reduction being less in subjects who complained of glare than in those who did not Yellow-tinted glass makes some drivers think that the visual field is brighter, but this impression is false such glass adversely affects their visual efficiency, especially at night Yellow-tinted lenses are particularly disadvantageous to colour defectives (Miles 1954) A clear-glass windscreen transmits about 92% of the light falling on it, while the lightest yellow filter passes only about 88% A combination of the two passes only about 81% under ideal conditions and considerably less when it is dirty or scratched (*British Medical Journal* 1954) The many problems of vision in relation to driving were discussed by Kelly et al (1955), with bibliography

In the absence of a precise method of relating visual acuity to the requirements of driving, various arbitrary standards have been recommended The American Medical Association (1959) regards a corrected vision of 20/40 as adequate for driving a private vehicle, those with vision less than 20/40 should be referred to an ophthalmologist. At present there is no uniformity of opinion about visual acuity between 20/40 and 20/70 Patients with less than 20/70 corrected vision in the better eye should be advised not to drive The British Medical Association (1954) recommends that drivers of public-service and heavy vehicles should have a minimum corrected visual acuity of 6/9 in one eye and 6/24 in the other, but makes no recommendation for private-vehicle drivers The World Health Organisation (1956) says that drivers of heavy vehicles should have a corrected visual acuity of at least 1 6 for both eyes together, for drivers of light vehicles (including private cars) their minimum is 0 8

Davey (1958) recorded the visual acuity of 1534 private-car drivers who consulted opticians in this country because of difficulty in seeing (often presbyopia) 5 drivers had a binocular corrected visual acuity lower than 6/18—worse, that is, than the " number plate reading at 25 yards " standard required for the issue of a

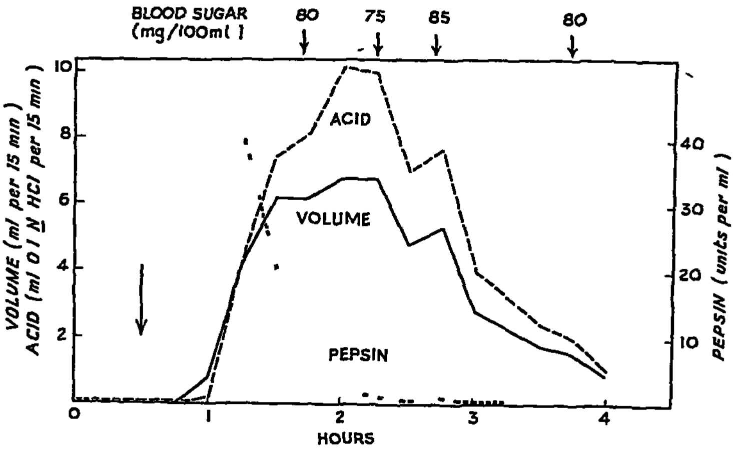

Fig. 1 (dog no. 1)—Response of the denervated fundic pouch to the subcutaneous injection of the first tumour extract (at 30 minutes). Blood-sugar values at times indicated by arrows.

In the last 5 years more than a hundred cases of the "Zollinger-Ellison syndrome" have been recorded. However, in no case so far reported has gastric secretion been studied on the intact stomach before and after removal of a pancreatic tumour, and apparently no attempt has been made to extract from such a tumour a substance capable of stimulating gastric secretion.

The observations reported here were made on a tumour of the pancreas removed by Prof. F. A. R. Stammers from a case of the Zollinger-Ellison syndrome admitted to the medical unit of the Queen Elizabeth Hospital, Birmingham. Full details of the case, and the clinical and pathological investigations, will be reported separately (French and Stammers 1960). The present communication is concerned with the biochemical and physiological investigations on the tumour.

The patient, a man aged 55, presented with episodic dyspepsia and diarrhœa and was found to have a duodenal ulcer, œsophagitis, and steatorrhœa. Basal and nocturnal gastric acid secretions were found to be elevated to levels commonly associated with the Zollinger-Ellison syndrome, and the pH of secretions aspirated from the distal duodenum frequently lay between 1·0 and 1·5. A presumptive diagnosis of the Zollinger-Ellison syndrome led to laparotomy, and a small tumour attached to the head of the pancreas was found and removed. No other surgical procedure was carried out. The patient became free of symptoms from the first postoperative day.

Immediately after removal, two-thirds of the tumour (about 2 g) was cooled to −70°C, and thereafter it was kept deeply frozen until used for the investigations described below. The remaining third was examined histologically and found to be an islet-cell neoplasm.

Experimental

In collaboration with Prof. W. L. M. Perry and Dr. H. M. Adams of the department of pharmacology, University of Edinburgh, a simple extract was made from 600 mg. of the tumour by homogenisation in Tyrode's solution. The histamine activity of the homogenate was found to be less than 0·25 µg. base per gramme of fresh tissue. Varying amounts of this extract were infused into the anæsthetised rat preparation of Ghosh and Schild (1958) and injected intravenously into a conscious Heidenhain-pouch dog. No evidence was obtained of the presence in the extract of a stimulant of gastric secretion, and no pyrogenic or other toxic effects were observed.

It was argued that if the tumour did in fact contain a stimulant of gastric secretion, this might be similar in chemical nature to the antral hormone gastrin, since, in order to enter the general circulation and so cause the gastric hypersecretion observed clinically, it must first survive passage through the liver, as does gastrin. It was therefore agreed to extract a portion of the tumour by a method shown to be successful for the preparation from hog antral mucosa of the hormone gastrin. Another portion of the tumour, weighing 800 mg., was accordingly thawed, minced finely with rather more than its own weight of moist picric acid crystals, and sent by post to Liverpool for further treatment.

The method used was adapted from that recently evolved by Gregory and Tracy (1959) for the extraction of gastrin from hog antral mucosa.

This method (soon to be published in full) provides an extract which is free from histamine, but which, like the antral hormone, stimulates the secretion of gastric acid, but not of pepsin. The extract, in contrast to those hitherto described, has been found effective when injected subcutaneously into conscious dogs, as well as intramuscularly or intravenously.

The method commences with treatment of the fresh tissue with picric acid, and it has been found (Gregory and Tracy, unpublished) that at this stage gastrin activity survives for some days at least under conditions of simple refrigeration or even at room temperature. In the present instance this fact was of great advantage, since it made possible convenient transport of the tissue without loss of activity.

The mixture of tumour and picric acid was ground with fine sand and then extracted overnight at room temperature with

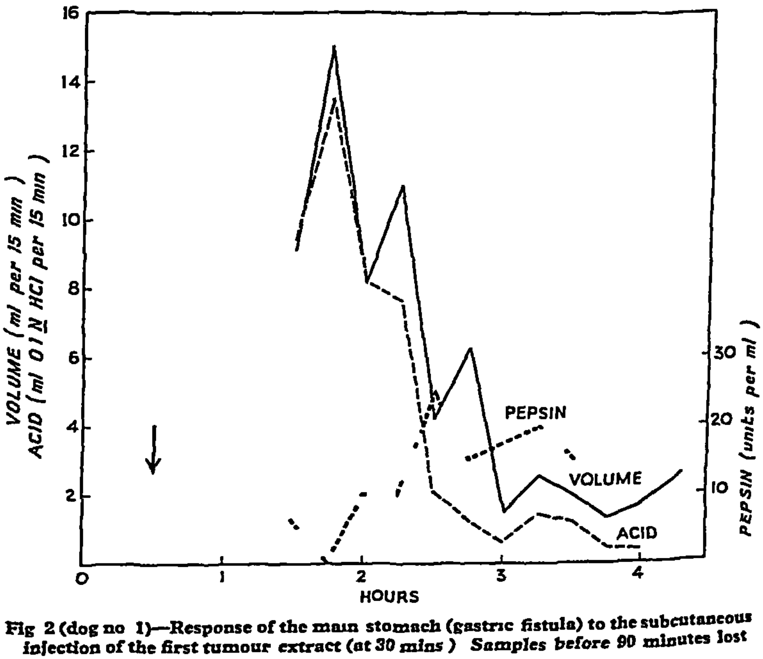

Fig. 2 (dog no. 1)—Response of the main stomach (gastric fistula) to the subcutaneous injection of the first tumour extract (at 30 mins.). Samples before 90 minutes lost. Same experiment as in fig. 1.

an excess of acid aqueous acetone The acetone and acid were removed and the aqueous residue precipitated and washed with trichloracetic acid solution The precipitate was then dissolved and inert protein removed The final product was a clear solution (5 ml) having a pH of 8·2, in approximately 0·9% NaCl solution

This extract was given as a single subcutaneous injection to a fasting conscious dog (dog no 1) provided with a gastric fistula and also a completely denervated fundic pouch (Gregory 1958) After about 15 minutes there ensued a large and prolonged secretory response from the pouch (fig 1) The main stomach also secreted, though to a lesser degree, having regard to the relative size of the stomach and the pouch (fig 2) This disparity between the main stomach and the pouch was also shown by this dog in response to injections of gastrin and of histamine, and is probably attributable to the fact that the gastric fistula had been prepared more recently than the pouch.

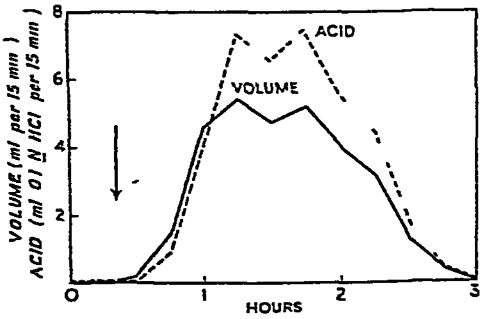

Fig 3 (dog no 1)—Response of the denervated fundic pouch to the subcutaneous injection of a gastrin extract equivalent to 20 g fresh hog antral mucosa (at 20 minutes)

The total amount of acid secreted by the pouch in response to the tumour extract, during the 210 minutes for which secretion lasted, was 6·71 mEq HCl There was no stimulation of pepsin secretion in either the pouch or the main stomach, and the animal's blood-sugar remained unchanged There were no effects on respiration, heart-rate, or general behaviour

The response of the denervated pouch in the same dog to a subcutaneous injection of gastrin equivalent to 20 g of fresh hog antral mucosa, prepared by the method on which the extraction procedure used for the tumour was based, is shown in fig 3 The total amount of acid secreted by the pouch was 3·73 mEq HCl, so that, comparing the responses, the tumour was 45 times as active in stimulating secretion as an equal weight of hog antral mucosa The reponses shown to gastrin and to the tumour extract, both by the pouch and the main stomach, were closely similar, and quite different in pattern from the response of the same dog to a subcutaneous injection of 1 mg histamine acid phosphate (fig 4)

In the same dog, the subcutaneous injection of 20 units of soluble insulin caused a considerable secretion of acid and pepsin from the main stomach, but no detectable response from the denervated pouch (fig 5) This, together with the fact that the blood-sugar level did not change after injection of the tumour extract, excludes any possibility that its effect on the pouch was due to the presence of insulin.

The remainder of the tumour (425 mg) was now treated with picric acid and despatched as before, on arrival in Liverpool it was extracted in precisely the same manner as the first portion One-tenth of the final solution (0·5 ml , corresponding to 42·5 mg fresh tissue) was set aside for testing on the blood-pressure of the anæsthetised cat, the remainder was injected subcutaneously into a dog (dog no 2) different from the one previously used This animal was provided only with a denervated fundic pouch The extract was injected subcutaneously at two sites There followed a considerable secretory response, which was of more prompt onset (less than 15 minutes) but more prolonged, than in the first dog (fig 6), the total amount of acid secreted during the 285 minutes for which the response continued was 3·2 mEq HCl The undulatory character of the response is probably attributable to some variation in the rate of absorption from the two sites of injection. As before, there were no side-effects

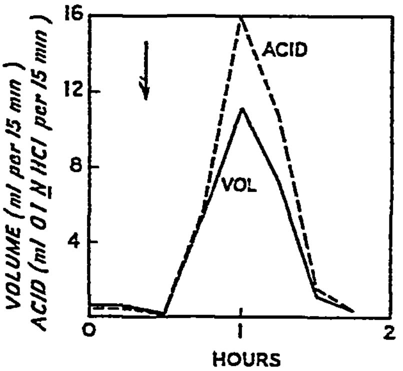

Fig 4 (dog no 1)—Response of the denervated fundic pouch to the subcutaneous injection of 1 mg histamine acid phosphate (at 20 minutes)

On another occasion, this dog was injected subcutaneously with the same amount of the same gastrin preparation as had been given to the first dog, it secreted a total of 4·87 mEq HCl Comparing these responses, the tumour was 33 times as active in stimulating secretion as an equal weight of hog antral mucosa This is in reasonable agreement with the factor of 45 calculated on the basis of the first experiment in dog no 1

That the effect of the extract was unlikely to be due to the presence of histamine seemed clear from (1) the negligible histamine activity of the simple saline homogenate originally made, (2) the fact that the extraction procedure used involved precipitation and washing with trichloracetic acid, and (3) the difference in form of the secretory response to the tumour extract and that produced by histamine in the same dog Nevertheless, the aliquot of the extract which had been saved was diluted with an equal volume of 0·9% NaCl solution and used

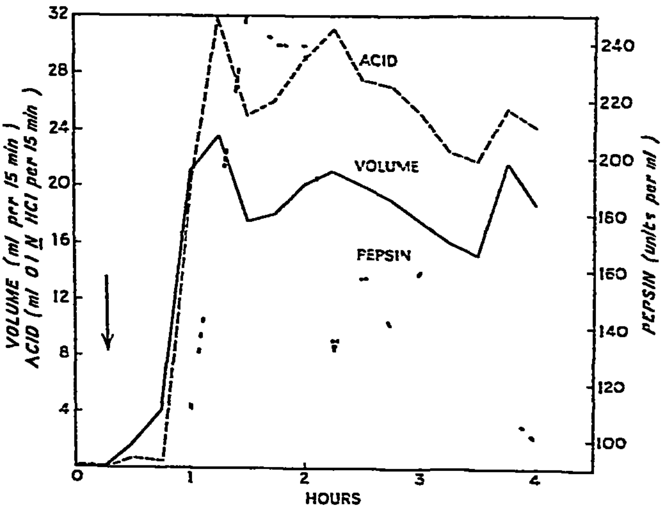

Fig 5 (dog no 1)—Response of the main stomach (gastric fistula) to the subcutaneous injection of 20 units soluble insulin (at 15 minutes) The denervated fundic pouch did not secrete

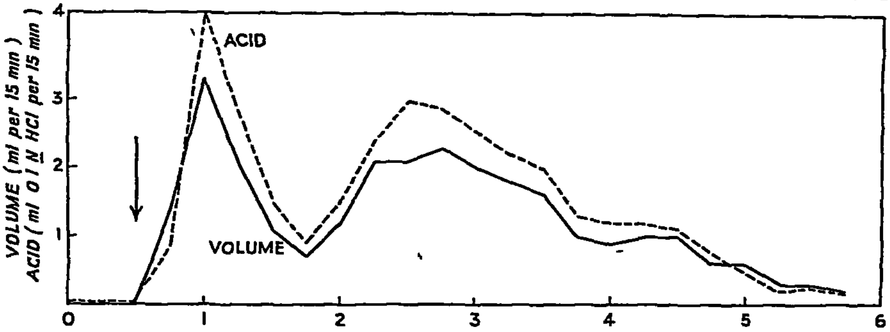

Fig 6 (dog no 2)—Response of the denervated fundic pouch to the subcutaneous injection (at 30 minutes) of the second tumour extract

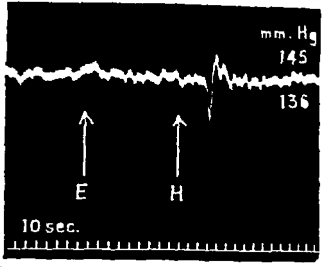

Fig 7—Effect on blood-pressure of an anæsthetised cat of intravenous injection (at E) of an aliquot of the second tumour extract equivalent to about 20 mg fresh tissue. At H, intravenous injection of 0 25 µg histamine base

for two intravenous injections into an anæsthetised cat (fig 7) There was no significant vasodilator effect, whereas a similar injection of 0 25 µg of histamine base caused the usual sharp and considerable fall in blood-pressure Thus the extract contained no detectable amount of histamine, nor did it cause the release of histamine on intravenous injection

Discussion

These experiments establish that the tumour extract contained a substance which in its chemical and physiological properties resembled the antral hormone gastrin Its activity was not due to histamine or insulin, nor did it cause the release of histamine on intravenous injection The amount of gastrin-like activity found in the tumour was many times greater than that which can be extracted from fresh hog antral mucosa by the method on which the procedure used for the tumour was based

The present findings do not establish that the active principle in the tumour extract was in fact gastrin, but they do establish that it must have been a substance of similar chemical nature, and that its effects on the secretion of gastric acid and pepsin were identical with those shown by gastrin in similar circumstances The amount of tissue available was too small for any further comparison between the chemical properties of the active principle and that of gastrin, but this might be possible in the future

One question which obviously arises is whether normal pancreas contains a similar gastrin-like substance The method described has not been applied to normal human pancreas, but Gregory and Tracy (unpublished) have not succeeded in extracting any such activity from fresh hog pancreas

So that examination of similar tumours in the future shall be as fruitful as possible, it seems worth emphasising (*a*) that attempts to demonstrate secretogogue activity in simple saline extracts are unlikely to succeed, and (*b*) that the activity survives at least several days, even at room temperature, once the fresh tissue has been thoroughly impregnated with picric acid

Conclusion

The pancreatic tumour from a patient with the Zollinger-Ellison syndrome has been shown to contain large amounts of a substance which in its chemical and physiological properties resembles the antral hormone gastrin

Two preparations made from the tumour by a method which extracts gastrin from hog antral mucosa stimulated the secretion of gastric acid, but not of pepsin, when injected subcutaneously into conscious dogs

The activity of the preparations was not due to the presence of insulin or histamine

We wish to thank Prof W L M Perry and Dr H M Adams of the department of pharmacology, University of Edinburgh, for their kind assistance with the initial treatment of the tumour

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FATTY FOODS AND OBESITY

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ASSISTANT PHYSICIANS

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In several recent reports a diet containing much fat but little carbohydrate has been advocated for reducing the weight of obese patients This principle is not new, it was mentioned in 1932 by Lyon and Dunlop, and later by Pennington (1954) But not until Kekwick and Pawan's experimental studies (1956) were published did the high-fat reducing diet begin to attract attention in the popular press in Britain and Scandinavia (Mackarness 1958)

The suggestion was that if the diet is sufficiently low in carbohydrate (less than 60 g a day), the obese patient will lose weight even if the calorie intake considerably exceeds that of the composite diet on which he had previously remained overweight This can of course only be true if the fatty food is capable of augmenting energy expenditure Kekwick and Pawan (1956), whose conclusions were far more guarded than those of their journalistic followers, accepted the existence of such a " luxury consumption ", believing that energy expenditure is increased by proteins and especially by fats, whereas it is decreased by carbohydrates The crucial point of their work was the observation that four out of five obese patients lost 1–2 6 kg when, for a week, a normal composite diet of 2000 calories was replaced by a diet of 2600 calories given mainly as fat and protein In another experiment fourteen obese patients were given, in successive weeks, three different diets, each of 1000 calories, of which carbohydrate, protein, or fat comprised 90% Most weight was lost with the high-fat diet, the high-protein diet was somewhat less effective, and little or no weight was lost on the high-carbohydrate regimen

When we planned the following study, it was clear that some of the questions raised by reports on the effect of a fatty diet did not require new experimental studies, because they could be answered by generally accepted physiological facts. Classical reports on the specific-dynamic action of foodstuffs do not point to any increase of metabolism due to fat; on the contrary, the action of fat seems to be smaller than that of carbohydrate, and this has recently been confirmed by Hawthorne et al. (1956). Swift et al. (1959) found no appreciable difference in the energy utilisation by man of equicaloric diets containing widely different amounts of fat. We know, moreover, that an intact digestive canal absorbs large quantities of fat as effectively as it does normal amounts. This leaves the possibility that the weight fluctuations observed by Kekwick and Pawan (1956) are due to alterations in the body's fluid content. Kekwick and Pawan tried to check this possibility by determining total body-water, and they found that the ratio body-weight/body-water remained remarkably constant during weight loss on the various diets.

The fact that some of Kekwick and Pawan's obese patients temporarily maintained their weights on high carbohydrate diets yielding as little as 1000 calories (which is decidedly lower than the basal metabolism of a euthyroid adult) while others lost weight on high-fat diets containing as much as 2600 calories, seems to us to be the best indirect argument against Kekwick and Pawan's main premise—namely, that the proportion of water in body-weight is unchanged. Their data reveal, not surprisingly, that some patients lost considerably less water than the average 30–50% of the weight loss, while others augmented their total body-water content despite weight losses of up to 3·6 kg. In some the loss of water was much greater than the average, and in a few the water loss exceeded the loss of body-weight. This can only mean that the method of determining total body-water was too inaccurate to allow safe conclusions regarding fluctuations in body-fluid during short observation periods.

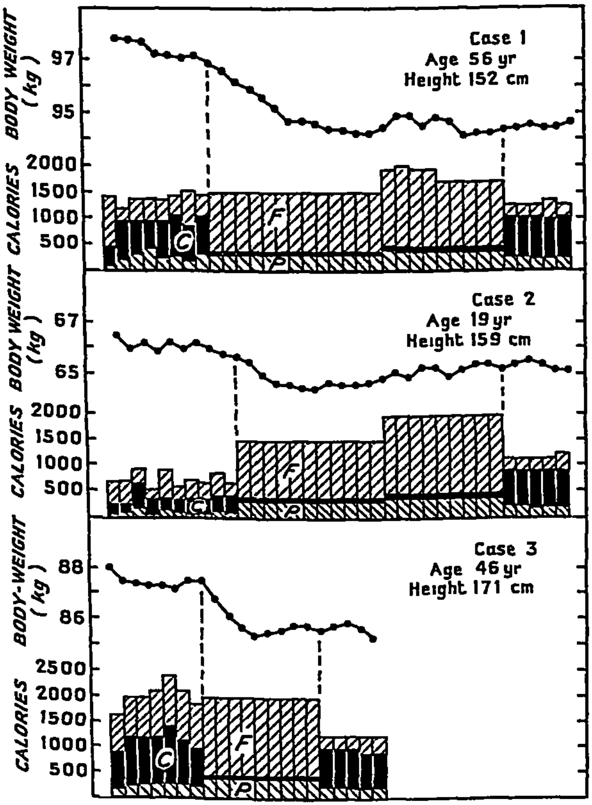

Fig 1—Body-weight of cases 1-3 on a normal composite diet, on a high-fat/low-carbohydrate diet (1500-2000 calories), and on a high-carbohydrate/low-calorie diet.

F = fat, C = carbohydrate, P = protein.

The Investigation

We studied eight female volunteers, with various degrees of obesity but no other disorder thought to be relevant.

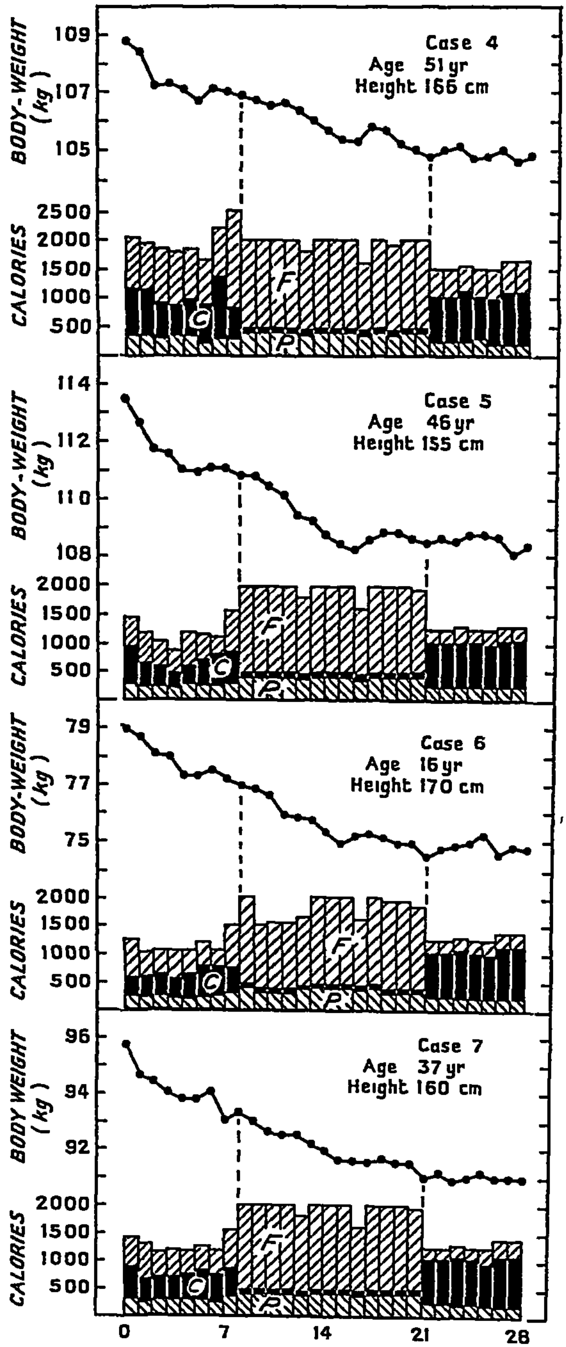

Fig 2—Body-weight of cases 4-7 on a normal composite diet, on a high-fat/low carbohydrate diet (about 2000 calories), and on a high-carbohydrate/low-calorie diet.

F = fat, C = carbohydrate, P = protein.

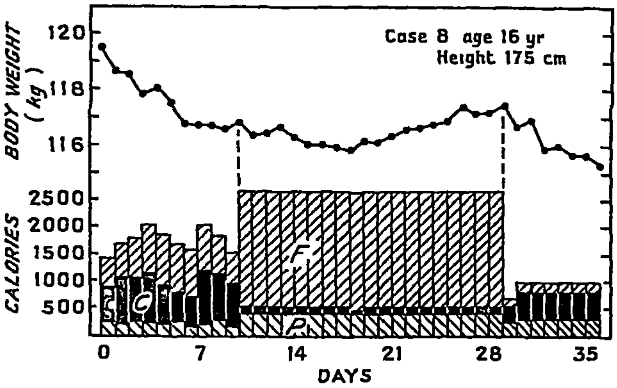

Fig 3—Body-weight of case 8 on a normal composite diet, on a high-fat/low-carbohydrate diet (2600 calories), and on a high-carbohydrate/low-calorie diet
F = fat, C = carbohydrate, P = protein

The patients remained in hospital under strict control throughout the observation period, but they were not kept in bed They were weighed at the same time every morning, fasting and naked, after they had passed water but not defæcated For the first few days we gave them ordinary composite food ad libitum The meals were prepared in a special kitchen from weighed ingredients, the individual helpings and what might be left over were weighed, and the intake was calculated in terms of calories, protein, fat, and carbohydrate

Their spontaneous food intake was considerably smaller than that regarded as necessary for maintaining energy balance The initial weight-loss subsided after 5–8 days, and body-weight was tolerably stable when we altered the diet (fig 1)

We next gave them less than 25 g of carbohydrate daily, the rest of the calories being divided between protein and fat in the proportion of about 1/5 Of this fatty diet the first two patients (cases 1 and 2) consumed 1500 calories daily For case 1 this corresponded to the spontaneous intake in the initial period Their weights decreased during the next 5–7 days, and then they again stabilised themselves During the next 9 days, when the patients had an intake of about 2000 calories from the high-fat diet, case 2 gained about 1 kg while the weight of case 1 did not change significantly The third patient (case 3) was given a 2000-calorie high-fat diet directly after the free-fare period, corresponding to her initial spontaneous calorie intake, she too had a striking loss of weight during the first 5 days and then her weight stabilised itself

A similar pattern was found in the next four patients (cases 4–7) who, for 13 days, took about 2000 calories daily as a fatty diet (fig 2)

During the last 5–7 days of the observation period all seven patients had about 1250 calories daily in the form of a diet relatively high in carbohydrate (about 60% of the calories), and all their weights remained practically unaltered Their basal metabolic rates showed that this calorie intake was less than their minimum energy requirements, and it must therefore be assumed that they had drawn on their energy stores during this period The fact that their weights were unchanged can only be explained by water retention—possibly connected with glycogen storage Our 1250-calorie diet was only relatively rich in carbohydrate, containing if anything less carbohydrate than normal food If, as we think is inevitable, one assumes that our patients retained water on this moderate carbohydrate intake, then it must follow that they were in a state of relative dehydration during the preceding period The weight loss during the first 5–7 days of the fatty diet seems to reflect this dehydration Thus the initial weight loss associated with the high-fat diet is not, in our opinion, due to a reduction of the fat deposits, and it cannot be termed "slimming" in the accepted sense of this word

OXYGEN CONSUMPTION DURING REST AND DURING STANDARDISED *MUSCULAR EXERTION ON A NORMAL COMPOSITE DIET, AND ON A* HIGH-FAT/LOW-CARBOHYDRATE DIET

Case no	Diet	Metabolism (calories per min)		Ratio Metabolic increase (calories per min) / Body-weight (kg)
		At rest	At work	
1	Normal " Fatty " "	1·18 0·95 1·16 1·02 1·10	3·54 3·51 3·53 3·55 3·71	0·026 0·028 0·025 0·027 0·028
2	Normal " Fatty " "	1·02 0·93 0·92 0·98 0·89	2·82 2·58 2·47 2·31 2·30	0·028 0·025 0·024 0·020 0·022
3	Normal Fatty "	1·15 1·09 1·16	3·20 3·38 3·20	0·023 0·026 0·024
4	Normal Fatty	1·07 1·20	3·47 4·00	0·022 0·026
5	Normal Fatty	1·27 1·42	5·05 4·44	0·033 0·028
6	Normal Fatty	1·26 1·20	3·38 3·02	0·027 0·024
7	Normal Fatty	1·26 1·15	4·12 3·90	0·030 0·030
8	Normal Fatty	1·29 1·44	4·52 4·52	0·028 0·027
Average	Normal Fatty	1·14 1·13	3·62 3·42	0·027 0·026

Our last patient (case 8, fig 3) was the only one able to consume as much fatty food (2600 calories a day) as was given by Kekwick and Pawan (1956) For 19 days she took this diet, which contained 40 g of carbohydrate Like the other patients she lost weight during the first week and then she began to gain This was hardly surprising considering the calorie value of the food, and the increase in weight must have been due to deposition of fat She was afterwards given 1000 calories a day of a diet relatively high in carbohydrate (50%), and her weight began to decrease The reason she did not maintain her weight like the other patients

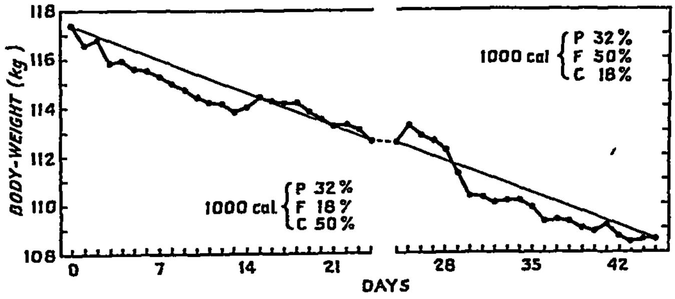

Fig 4—Body-weight of an obese patient (case 8), who for 45 days consumed 1000 calories a day—as a carbohydrate/low-fat diet during the first 24 days, and as a low-carbohydrate/high-fat diet during the last 21 days
F = fat, C = carbohydrate, P = protein

during this stage of the experiment, seems to be that her calorie deficit was too great to permit glycogen deposition and rehydration

To throw light on whether a fatty diet poor in calories causes more weight to be lost than an equicaloric high-carbohydrate diet, we gave case 8 1000 calories (32% protein) daily for 45 days, with 50% carbohydrate and 18% fat during the first 24 days, and 18% carbohydrate and 50% fat during the last 21 days (fig 4) The weight curve wavered somewhat, but not systematically, and on each diet the weight loss after 21 days was exactly the same—namely, 4 1 kg

Discussion

Our patients are too few to allow far-reaching conclusions, but all the same we believe that our observations do carry certain weight, partly because of their uniformity and partly because our observation periods were longer than those of Kekwick and Pawan (1956)

Our dietary experiments were supplemented with determinations of oxygen consumption during the periods of ad-libitum and of fatty diet Energy metabolism was computed as calories per minute, and determinations were made 3 hours after breakfast, first during rest and then during standardised muscular exertion which comprised stepping on and off a small stool at a fixed pace (table I) As might be expected, the figures vary from one determination to another, but they do not support the assumption that energy expenditure is higher on a fatty diet than on a normal food intake Because muscular exertion must vary with the body-weight at least, we divided the metabolic increase by the weight of the patient (right-hand column) The figure thus obtained does not vary appreciably for each patient, and it is of the same magnitude for the whole group

We should perhaps point out that this study does not answer the question of whether a high proportion of fat makes it easier for obese patients to restrict their calorie intake

Summary

Eight obese women were treated in hospital with the following successive diets

1 Plain composite food ad libitum for 7–10 days
2 A diet with a high-fat content, yielding 1500–2600 calories, and a carbohydrate content of 25–40 g for 9–22 days
3 A diet of low-calorie value (about 1250) but of comparatively high carbohydrate content for 5–7 days

We were led to the following conclusions

1 A high-fat/low-carbohydrate diet may reduce the weight of obese people considerably But this weight-loss ceases after a few days and it may be explained largely—perhaps wholly—by release of water from deposits in the body

2 Continued intake of a high-fat/low-carbohydrate diet affects body-weight in the way expected from the number of calories ingested

3 A diet containing a relatively high proportion of carbohydrate, but with a calorie intake below the theoretical minimum, may be compatible with a stable body-weight—at any rate if taken after a period of fatty diet This is most likely attributable to simultaneous increase of the body's fluid content

4 In a single experiment such a high-carbohydrate diet, continued for 3 weeks, produced a loss of weight which was identical with that produced, during the next 3 weeks, by an equicaloric high-fat diet.

5 The oxygen consumption of our obese patients, measured during rest and during standardised exertion, was no higher on a fatty diet than on an ordinary composite diet

References at foot of next column

CARBON-MONOXIDE DIFFUSION

SIMPLE TEST FOR ROUTINE CLINICAL USE

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Diffusion of oxygen from alveolus to pulmonary capillary is increasingly often measured by carbon-monoxide-diffusion tests in respiratory and cardiac disease, but, because the equipment is expensive and the tests are complex, these have so far been practicable only in specially equipped laboratories (Simpson 1959)

The test described here is suitable for use in any hospital laboratory or at the bedside

Apparatus

The apparatus consists of (*a*) two Douglas bags connected via a one-way valve so that the subject inhales from one and exhales into the other, and (*b*) a carbon-monoxide analyser (fig 1)

This is a palladosulphite carbon-monoxide detector (marketed by Siebe, Gorman & Co, Ltd, of Chessington, Surrey) comprising a simple aspirator pump for drawing the gas under test through an indicator tube, which contains silica crystals impregnated with potassium palladosulphite, which changes colour from an initial light yellow to a distinctive brown in the presence of carbon monoxide. The carbon-monoxide concentration is indicated by the length of brown stain produced, and is read from a calibrated chart The expendable tubes cost 3*s* 9*d* each

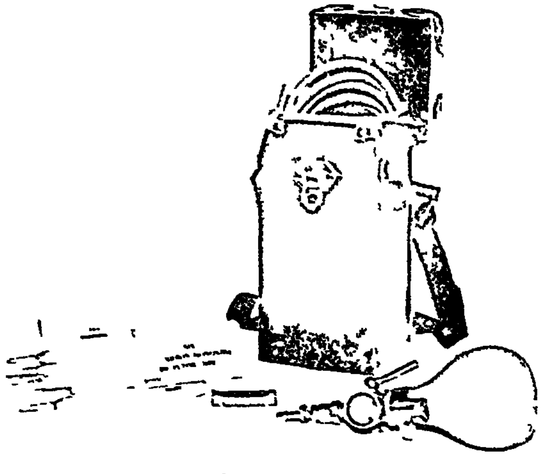

Fig 1—Palladosulphite carbon-monoxide detector

Procedure

The " inhale " Douglas bag is charged with about 50 litres of air or oxygen plus about 20 ml pure carbon monoxide or about 130 ml of coal gas, giving a carbon-monoxide concentration of approximately 0 04%

As the palladosulphite analyser has been developed for use with coal gas, this can be used as a source of carbon monoxide, and the taste and smell at such a concentration are hardly noticeable

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DR. OLESEN, DR QUAADE REFERENCES

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TABLE I—ESTIMATES OF CARBON-MONOXIDE CONTENT (%) OF VARIOUS GAS MIXTURES BY MEANS OF PALLADOSULPHITE ANALYSER COMPARED WITH RESULTS BY MEANS OF INFRA-RED ANALYSER

Reading from infra-red analyser	Palladosulphite analyser		
	Reading	Error	% error
0·026	0·0275	+0·0015	+ 6%
0·026	0·025	−0·001	− 4%
0·0386	0·035	−0·0032	− 9%
0·0386	0·035	−0·0032	− 9%
0·035	0·035	Nil	Nil
0·016	0·018	+0·002	+12%
0·045	0·049	+0·004	+ 9%
0·0184	0·017	−0·0014	− 8%
0·044	0·044	Nil	Nil
0·0177	0·017	−0·0007	− 4%

The patient starts to breathe the mixture, and the gas is sampled via the side tube of the bag. At the end of one minute the taps of the bags are turned off, and the expired gas is sampled. Finally the gas from the "expire" bag is run through a gasometer to give the minute volume, should this measure be required.

The carbon monoxide extracted, which is the difference between the concentration of inhaled and of exhaled gas, is expressed as a percentage of the inhaled gas carbon-monoxide concentration.

$$\text{Carbon-monoxide \% extraction} = \frac{\text{inhaled carbon-monoxide content minus exhaled carbon-monoxide content}}{\text{inhaled carbon-monoxide content}} \times 100$$

The test can easily be repeated, and duplicate estimations are probably advisable.

Assessment of Accuracy

Great care must be taken in reading the length of stain, and the criteria of stain length must be kept constant.

Four readings are taken round the circumference of the tube and averaged to give a single reading, since tubes sometimes do not stain evenly. An accuracy of ±0·5 mm should be possible.

The results of analysing various gas mixtures with the palladosulphite analyser and with an infra-red analyser are compared in table I. The results of simultaneous tests using the palladosulphite analyser and an infra-red analyser are shown in table II. In 10 cases in which per-cent extraction was measured in duplicate the maximum difference between the two readings was 10%, and the average difference 5·6%. Apparently it should be possible to obtain an overall accuracy of ±10%.

TABLE II—RESULTS OF SIMULTANEOUS ESTIMATIONS OF CARBON-MONOXIDE PER-CENT EXTRACTION BY MEANS OF PALLADOSULPHITE ANALYSER AND INFRA-RED ANALYSER

—	Infra-red analyser	Palladosulphite analyser	Difference
Normals			
1	54%	60%	+6%
2	61%	62%	+1%
3	54%	51%	−3%
4	61%	65%	+4%
5	61%	60%	+1%
Patients			
1	28·5%	33%	+4·5%
2	42%	38%	−4%
3	25%	26%	+1%
4	36%	33%	−3%

Results

Results in healthy persons and in patients with emphysema and pulmonary fibrosis are shown in fig. 2. This shows that the test discriminates reasonably well between normal and abnormal, and that in patients those with the greater incapacity have lower per-cent extraction values.

Our values for the 14 healthy subjects ranged from 43% to 65% with an average of 52%, which are the same as found by other workers (Bates 1952, MacNamara et al. 1959).

The average per-cent carbon-monoxide extraction in the 13 cases of diffuse pulmonary fibrosis was 34·5%, compared with 31·9% found in a similar group by MacNamara et al. (1959).

In the 9 cases of emphysema the patients were all disabled by their condition, and carbon-monoxide diffusion was considerably reduced.

Discussion

The results of diffusion measurements are usually expressed in physiological "absolute" values of millilitres per minute per millimetre of mercury—that is, as diffusing capacity—but MacNamara et al. (1959) have shown that expression of the results as per-cent extraction of carbon monoxide discriminates no less effectively between normal and abnormal diffusion.

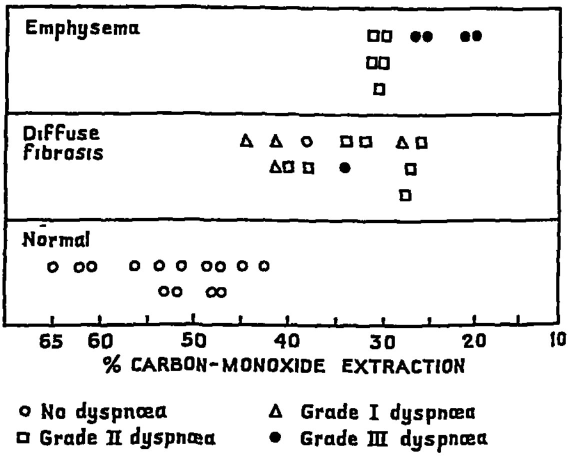

Fig. 2—Spot diagram showing distribution of values for percentage extraction of carbon monoxide in normals and in patients with diffuse pulmonary fibrosis and with emphysema.

By attempting to estimate only the carbon-monoxide per-cent extraction we avoid many of the difficulties involved in standard methods, such as end-tidal-air sampling or arterial puncture. Also, the per-cent extraction of carbon monoxide is unaffected by fairly wide variations in ventilation and tidal volume (Gilson and Hugh-Jones 1955, MacNamara et al. 1959), and therefore these need not be measured.

I am deeply indebted to Dr. W. M. Macleod for his help in the preparation of this paper, to Dr. J. G. Scadding, director of the Institute of Diseases of the Chest, where this method was compared with the standard diffusion test, and to Dr. F. J. Prime for his help and encouragement, to the Wessex Regional Hospital Board for facilities, to Mr. D. L. Williams, of the Southern Gas Board, for the loan of the analyser, and to my colleagues who acted as normal controls.

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"Thus an increase in the rate of change places an increasing strain on the machinery of democracy. This, I believe, is why democracy has broken down—or has not been attempted—in many countries where rapid industrialisation is taking place and why it is at risk everywhere. For when disturbance so overloads the adaptability of a system as to threaten its existence, the system is prone to take whatever steps seem likely to preserve its coherence. In the conflict between the urgent and the important, even freedom may seem a luxury."—SIR GEOFFREY VICKERS, *The Undirected Society*, p. 117. University of Toronto Press, 1960.

Preliminary Communications

INCREASED CUTANEOUS RESPONSE TO DILUTED AUTOLOGOUS SERUM IN HEREDITARY ANGIO-ŒDEMA

HEREDITARY angio-œdema—a rare highly fatal disease of unknown ætiology—is inherited as a mendelian dominant trait. Clinically it is characterised by frequently recurring attacks of acute circumscribed non-inflammatory œdema involving primarily the skin, subcutaneous tissue, larynx and gastrointestinal mucosa.[1,2] We report here the results of an investigation of the peculiar permeability-inducing properties of the serum[3,4] of a 32-year-old Caucasian woman affected with this disease since the age of 2.

The patient had a normal cutaneous response to 0·1 ml. intradermal injections of 1/10,000 histamine, acetylcholine, and 5-hydroxytryptamine. During episodes of angio-œdema, as well as during œdema-free periods, total blood histamine, the levels of 5-hydroxytryptamine, and acetylcholine esterase in the serum were normal, 24-hour blood-clots were not visibly lysed, and 24-hour urinary 5-hydroxy-3-indolacetic excretion was normal. Thus the level and metabolism of these endogenous substances, known to affect capillary permeability, were found to be normal as far as they were tested. When, however, attention was directed to the permeability-increasing factor(s) in diluted autologous serum,[3,4] a significant difference in the patient's reaction to her own diluted serum was noted.

The techniques used consisted in intravenous injection of Evans blue dye (T1824) 0·5 mg. per kg. body-weight, followed in 5 minutes by the intradermal injection of 0·1 ml. of undiluted human serum or serum diluted from 1/12·5 to 1/800 in physiological saline solution.[5] Serum dilutions were allowed to stand at room temperature for 30 minutes before the intradermal injection. If the injection of treated serum caused an increase of vascular permeability, a localised area of bluing resulted. The intensity and area of the bluing at the intradermal injection site measured 30 minutes after injection was used as an index of the vascular-permeability-increasing potency of the injected material.

Neither the patient nor the eleven normal subjects, six of whom were female, showed a significant bluing response to the injection of their own undiluted (autologous) serum. The patient, however, showed a response to the injection of her own serum diluted 1/12·5 to 1/800 which was significantly greater both in area and in intensity of bluing than was elicited in any of the eleven normal subjects to the injection of their own diluted serum. For example, at a dilution of 1/25 the average bluing diameter in the patient was 15·7 mm. with a range of 14–17·1 mm., while the mean diameter of the eleven normals was 11·3 mm. with a range of 10–12·5.

From three further experiments involving the patient and five normal controls, four of whom were female, it became apparent, however, that this increased reactivity was found only when the patient's own diluted serum was injected into the patient; neither the patient's diluted serum injected into normal individuals nor the diluted sera from the normal controls injected into the patient gave an increased response. A portion of the results of one of these three experiments is shown in the table. The invariable finding that the patient's own diluted serum reacted more strongly in her than did the sera of normal individuals is seen in the table, although the difference here is not as great as in other experiments. But the main point of the table is that the patient showed no increased reactivity to the control sera, nor did her serum react in the control subjects more strongly than the sera from normal individuals. Here again, this was the invariable finding in the experiments not shown.

CUTANEOUS RESPONSE OF PATIENT AND THREE CONTROL SUBJECTS TO INTRADERMAL INJECTION OF 0·1 ML. OF AUTOLOGOUS AND HOMOLOGOUS SERUM DILUTED 1/100 FOLLOWING INTRAVENOUS EVANS BLUE 0·5 MG. PER KG. BODY-WEIGHT

Recipient	Donor	Bluing response	
		Diameter (mm.)	Intensity
Patient	Patient	14·2	2+*
	A	9·9	1+†
	B	11·0	1+
	C	12·0	1+
Control A	A	8·8	±‡
	Patient	9·3	1+
	B	10·5	1+
	C	9·0	1+
Control B	B	11·1	±
	Patient	10·2	1+
	A	11·7	1+
	C	11·4	±
Control C	C	10·6	1+
	Patient	12·2	1+
	A	12·4	1+
	B	8·8	1+

* Deep blue. † Light blue. ‡ Faint blue.

The patient's two sons who have the disease were also studied, but less extensively. Both showed a significantly greater cutaneous bluing response to their own serum than did the eleven control subjects and both had a greater response to their own serum than to the diluted serum of a normal male control.

The nature of the agent in diluted serum responsible for the bluing was also investigated.

The response of the patient and normal control to injections of their own sera was completely inhibited by diluting their sera in crystalline soybean trypsin inhibitor 0·1 mg. per ml. before intradermal injection, or on the addition of the soybean trypsin inhibitor after the diluted serum had stood for 30 minutes.[3] The bluing response to diluted autologous serum was partially inhibited by diluting the serum in ε-aminocaproic acid 0·25 mg. per ml. before intradermal injection. No inhibition occurred if autologous serum was diluted in physiological saline, allowed to stand at room temperature for 30 minutes and then diluted in ε-aminocaproic acid to a final concentration of 0·5 mg. per ml.

There was no inhibition if the serum was diluted in the anti-histamine mepyramine maleate 0·1 mg. per ml., or in neostigmine. Diphenylhydramine hydrochloride ('Benadryl') 0·1 mg. per ml. inhibited the patient's response to dilutions of her own serum greater than 1/200, but did not inhibit a control's response. The patient's response to diluted autologous serum was depressed while under treatment with promethazine 200 mg. by mouth daily and this depressed response correlated with clinical improvement.[6]

From these experimental data, we postulate that the disordered vascular permeability in hereditary angio-œdema is an inherited hyperresponsiveness of the skin and other tissues to an autologous serum factor which, upon activation in vivo by an unknown stimulus, increases the permeability of capillaries.

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soon as the disease is diagnosed, and an authority is quoted as recommending (in 1941) the immediate institution of external drainage, but in the section on prognosis a more recent authority is quoted as stating that surgery is increasingly less needed, and that resection has replaced drainage when it is

The mustiness noticeable in some parts of the section on diseases of the chest is nowhere apparent in the chapters on cardiovascular disease recent advances are in fact, featured prominently There is a detailed and valuable discussion of the diagnosis of congenital cardiac malformations in infants and young children, and a useful and well-illustrated account of developments in cardiac surgery Among some first-class contributions on other topics, the chapter on radiology of the heart is outstanding As the respiratory and cardiac sections are in no way interdependent, there seems no advantage in publishing them in one rather unwieldy volume

Much of this book is excellent, but it will fall short of the highest standard until the approach to some of the subjects is more up to date and, above all, more critical, at present it cannot be unreservedly recommended

Textbook of British Surgery

Vol IV Editors SIR HENRY SOUTTAR, D M, F R C S, consulting surgeon, The London Hospital, J C GOLIGHER, CH M, F R C S, professor of surgery, University of Leeds London Heinemann Medical Books 1959 Pp 699 105*s*

THIS is the final volume of a series whose preceding parts have been warmly welcomed It contains some twenty articles on such topics as wounds, burns, fractures, and bone and joint diseases, and could well have been subtitled A Comprehensive Textbook in Practical Orthopædic Surgery The names of the seventeen contributors are sufficient warranty of its status While most similar encyclopædias contain a chapter on fractures, the subject is commonly dealt with in a highly compressed style which is, at the best, indigestible and, at the worst, positively misleading, so Mr John Clark is to be particularly congratulated for the way he has here discharged a difficult commission in only 70 pages The emphasis throughout is on the practical aspects

Biographical Memoirs of Fellows of the Royal Society 1959

Vol 5 London The Royal Society 1959 Pp 280 30*s*

THE latest addition to this splendid series contains, among 19 biographical studies, only 1 of a medical man, Robert Muir Others have had medical connections, W R G Atkins was for a time a captain in the R A M C and in 1942 did much routine physiological testing at medical centres throughout the country, resulting in papers on the vitamin-C reserves of troops and kindred matters G M Bennett in his early years was senior demonstrator in the department of chemistry at Guy's K S Lashley, an American psychologist, wrote an important monograph on *Brain mechanisms and intelligence a quantitative study of injuries of the brain* "It was a beautifully economical summing up of his experimental work of the preceding nine years It quickly achieved wide recognition, and whatever may eventually prove to be the finally correct story in detail of the nervous mechanisms and their functions involved in intelligent behaviour, it is certain that Lashley's work and his exposition in this monograph will remain of fundamental importance"

Sir Roy Cameron's 25-page biography of Robert Muir is splendidly done and is enriched with recollections by some of Muir's friends and assistants His scientific work fell into four clear-cut groups which are discussed in detail His earliest work faced the problem of where and in what manner the blood-cells were formed and how upsets in their development brought about disease This interest led to studies in immunity and later to the problem of hæmolysis His last work centred round the malignant cell

Each biography is preceded by a good portrait, and though some are illustrated with chemical formulæ and formidable equations, there are many light personal touches For example "As golfers, he (Muir) and I were of different species, he a tiger in his day and I a rabbit It wasn't until I joined his staff at the mature age of 30 I learned from him that proficiency in golf was essential to progress in pathology! In the 1920s and early 30s, he used to go to Newcastle, Co Down, with three other friendly tigers for a fortnight at Easter to play two rounds a day in all weathers—their aim in every round being to return a best-ball score of less than the average of their ages, i e., about 68 or less" Muir's biography alone makes this modestly priced volume essential for any medical library with a good reference section

At Your Best for Birth (and Afterwards)

EILEEN MONTGOMERY, M C S P Bristol John Wright 1959 Pp 59 5*s* 6*d*

THE author has set down the exercises which she recommends during pregnancy, labour, and the puerperium Great emphasis is placed upon relaxation as a means of avoiding tension, but Mrs Montgomery is very careful not to make any unjustifiable claims for relaxation exercises, and in her summing-up she acknowledges that, even without such training as she describes, childbirth can be quite a natural and pleasing experience The text is illustrated by excellent silhouette drawings The section on posture and on how to lift heavy objects is particularly good and the related drawings very helpful The patient is given sound advice on the correct shoes and clothes to wear during pregnancy A brief account is given of the anatomy, physiology, and management of labour The medical reader will be surprised to see a diagram likening the female pelvis to the flue of a chimney and to read that uterine action in labour is similar to that of the fingers squeezing a tube of toothpaste so that the contents are expelled These analogies are seldom very successful

In a small book the author has managed to include much that will contribute to the wellbeing of the pregnant woman The primigravida, in particular, will find useful information, common-sense, and good advice

Biochemical Values in Clinical Medicine

The Results Following Pathological or Physiological Change

ROBERT DUNCAN EASTHAM, M D, D C P, consultant pathologist to the Frenchay/Cossham group of hospitals, Bristol Bristol John Wright 1960 Pp 148 15*s*

THIS paper-backed pocket book provides a summary of the ways in which various conditions affect biochemical tests The investigations are arranged alphabetically for easy reference As far as possible the principle is explained, the normal range and physiological variation of the results given, and then follow the changes in disease The tests are not restricted to those normally performed by many routine laboratories Some are even given with the comment that they are not useful in clinical practice—for example, the estimation of blood and urine sulphate It is doubtful whether every reader will agree with all these comments There are a fair number of misprints amongst the references, and in the definitions the equivalent and milliequivalent weights of calcium are wrongly given This excellent compendium will be widely used, particularly on the ward.

Virus Virulence and Pathogenicity (*Ciba Foundation Study Group no 4* London J & A Churchill 1960 Pp 114 12*s* 6*d*)—A small group of virologists met in London to discuss a series of papers on virus virulence and pathogenicity with especial reference to influenza This book, edited by Dr G E W Wolstenholme and Miss Cecilia M O'Connor, contains the papers and verbatim discussions, and makes instructive and stimulating reading Although at the outset Stuart-Harris notes that it is practically impossible to measure virulence, this does not deter subsequent speakers Anyone interested in such topics as the reason for the differing mortality in the influenza pandemics of 1918 and 1957 or the use of living attenuated vaccines, will enjoy reading the lively discussions of this distinguished group

THE LANCET

LONDON 14 MAY 1960

Live Poliovirus Vaccine

INTEREST in attenuated poliovirus vaccines remains intense. This is because killed vaccine, though it is highly effective,[1] has certain deficiencies It is not 100% effective, frequent booster doses may be necessary, it is not proving easy to persuade enough people to receive the injections, and the vaccine is expensive. The case for living attenuated vaccine, which has been authoritatively expressed by PAUL,[2] is based on the belief that it will overcome these deficiencies It is thought that since orally administered attenuated virus will imitate natural infection by the natural route, almost lifelong and complete immunity will follow one dose of each type of poliovirus, and that the living virus will confer a local alimentary resistance to reinfection that is not conferred by killed vaccine It seems likely that resistance to the acceptance of vaccination will be overcome by an oral vaccine Attenuated vaccine should also prove cheaper to prepare and administer But these theoretical advantages have still to be proved in practice

A great deal more information about living vaccine has been published—notably in the full report of the First International Conference on Live Poliovirus Vaccines,[3] held in Washington last June Although attenuated vaccine has now been given to many millions of people without any recorded ill effects, neither its safety nor its effectiveness has been proved The doubts about safety concern not the vaccine strains themselves (though the conditions of manufacture and testing are necessarily severe in order to ensure the genetic stability of the vaccine strain and the exclusion of contaminating microorganisms) but rather the strains excreted by those vaccinated Excreted virus can spread to others—and indeed this capacity to spread has been used as an argument for attenuated vaccine since in this way people unwilling to be vaccinated may be protected It is now clear that the polioviruses excreted by the vaccinated sometimes differ from the virus fed They may show an increase in monkey neurovirulence, in ability to grow at high temperatures (40°C), or in ability to grow in low concentrations of sodium bicarbonate [4], and they may possibly show minor changes in antigenic structure [5] There is no evidence that virus with a greater neurovirulence for monkeys has a selective advantage in the human intestinal tract, nor is there evidence that harm has resulted from such changes Neurovirulence for the monkey displayed after direct inoculation into the central nervous system may bear little relation to virulence for man infected by mouth, where neurovirulence will manifest itself only if the virus is invasive enough to reach the central nervous system Nonetheless, the virus being mutable, it could possibly yield a mutant capable of causing epidemic disease in man, and this is presumably how virulent strains arise in Nature from less virulent wild strains

The uncontrolled spread of attenuated vaccine virus in man could be limited to some extent by administering the vaccine to newborn babies This would have other advantages The emergence of epidemics of poliomyelitis is probably due to postponement of poliovirus infection, because of better hygiene, till later in childhood when the antibodies acquired from the mother have declined and an increased biological sensitivity to poliovirus has been acquired Thus probably more than 99% of children would be benefited by infection with any wild type of poliovirus, let alone an attenuated one, in the first year or two of life It has been calculated [6] in Sweden that under the age of 5 years about 3 type-1 poliovirus infections in 1000 are paralytic, whereas over the age of 25 the risk of paralysis is 20–100 times greater The mortality also rises sharply with age—a point that should reinforce the present campaign to vaccinate people aged 26–40 Even during severe epidemics the incidence of paralysis in children has been found to be only 1–2 for every 100 infections Thus, the younger children are when they are vaccinated the less danger there is Other host factors besides age affect the outcome of poliovirus infection, and in mass campaigns there must always be some possibility, however remote, of causing a paralytic infection in someone of particularly great susceptibility due to physiological or genetic causes But in view of the impressive record of safety, mainly in Russia, with the attenuated vaccines, these dangers are probably exceedingly remote and hypothetical The difficulties in the assessment of the safety of living vaccine are clearly brought out in a study carried out in Leopoldville in the Belgian Congo [7-9] Here the CHAT strain of attenuated type-1 poliovirus was administered in a mass campaign to children under 5 years starting in August, 1958 Shortly thereafter a severe epidemic due to type-1 poliovirus occurred in the city The authors concluded that the vaccine was safe and about 60% effective in preventing paralysis—although, unfortunately, the vaccination campaign did not prevent the development of an epidemic. The vaccine was thought to be safe because the first cases appeared in unvaccinated patients who had had no known contact with vaccinated children Also the genetic and serological characters of CHAT virus and virus excreted by some who did not become ill differed from the characters of viruses isolated from cases Unfortunately, all the observed differences in characters have also been observed in attenuated polioviruses after passage in the human intestinal canal [4 5] The balance of evidence suggests that the epidemic strain was a naturally occurring poliovirus, but the possibility that

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1 See *Lancet* Jan 9, 1960, p 97

2 Paul J R *Yale J Biol Med* 1960 32, 241

3 Live Poliovirus Vaccines papers presented and discussions held at the First International Conference on Live Poliovirus Vaccines Washington D C. June 22–26, 1959 Pan American Sanitary Bureau, Regional Office of W.H O, Washington $5

4 Melnick, J L., Benvesh-Melnick, M, Brennan J C *J Amer med Ass* 1959, 171, 1165

5 Gard, S *Bull Wld Hlth Org* 1960 22, 235

6 Olin G Cited by S Gard *in* Live Poliovirus Vaccines p 228

7 Lebrun, A, Cerf, J Gelfand H. M Courtois G, Plotkin S A, Koprowski, H *Bull Wld Hlth Org* 1960, 22, 203

8 Plotkin, S A. Lebrun A, Koprowski H *ibid.* p 215

9 Koprowski H Norton, T W, Wecker E, Gard, S *ibid* p 243

turbances are those which in animal experiments result from reducing the number of surviving nephrons This is most easily understood in connection with substances excreted predominantly by glomerular filtration, such as urea and creatinine a decrease in the number of nephrons must result in retention in the body-fluids, if the rate of acquisition remains constant as the plasma levels rise, the filtered load per residual nephron increases until a new equilibrium is reached For most other functions it is difficult to define the capacities of nephrons in diseased kidneys, since, once a patient has Bright's disease, data can no longer be compared with control observations on the same subject, the chemical changes already present may affect the function of various parts, and finally there may be partly damaged nephrons with either glomerulus or tubules acting normally and the other part disordered, thus upsetting the whole basis of functional controls

Bricker et al [4] have now reviewed their experiments in which these difficulties have been overcome In dogs in which two separate urinary bladders had been formed they induced unilateral chronic chemical nephritis, chronic pyelonephritis, and chronic glomerulonephritis and in each series compared the function of the diseased kidney with the normal on the other side under various test conditions while the internal environment was kept essentially normal The various series all showed an absolute decrease in values for all renal functions in the experimental kidney But the functional capacity of the remaining nephrons was unimpaired thus the ratio of the glomerular filtration fraction to the effective renal plasma-flow, the maximum rate of secretion of *p*-amino-hippurate, and the maximum rate of glucose reabsorption were all the same, in the three types of diseased kidneys, as in the normal controls—suggesting that no anomalous nephrons were present Similarly, studies on the concentrating and diluting mechanisms of the diseased kidneys showed that these remained virtually intact, but the fewer the remaining nephrons the more advanced were the adaptive changes, the chief adaptation being a greater rate of solute excretion per nephron leading to relative isosthenuria The patterns of excretion for sodium, chloride, and potassium were all similar in the diseased kidney to those in the normal, with remarkable ability to maintain normal plasma concentrations From comparison of these findings with the series of events in chronic renal failure, Bricker et al concluded that the diseased kidneys have a gradually diminishing number of nephrons, but that these retain normal functional capacity, that the functional changes relate to adaptive changes imposed by the decreased number of nephrons and resultant changes in body-fluids, that the flexibility of function decreases as the number of nephrons decreases, and that this occurs in an orderly and predictable pattern

In a comprehensive review of pyelonephritis, Kleeman et al [5] point out that, while the pathological changes in the chronic pyelonephritic kidney are complex and pleomorphic, the functional patterns for the remaining nephrons are more or less normal the most reasonable explanation is that the majority of renal glomeruli and tubules, severely altered by the disease processes, are non-functioning while the tests measure the relatively normal function of the residual units and show no glomerulotubular imbalance

Thus chronic renal failure should not be regarded as a haphazard series of disordered functions resulting from haphazard lesions of different parts of nephrons, and, as Platt [3] recommended, the aim in treatment should be to reduce the work of the kidney by restricting protein intake but giving liberal amounts of salt and of water, for the last of which the patient's instinctive demands are usually the most accurate guide

CEREBELLAR CORTICAL DEGENERATION IN ALCOHOLICS

NEARLY a hundred years ago Samuel Wilks [6] noted that heavy drinkers of brandy, or of "the diabolical compound called absinthe" across the Channel, were liable to become paraplegic although sometimes the symptoms were "almost confined to the legs, resembling in character, those of locomotor ataxia" He believed that in these patients the volatile oils dissolved in the alcohol had given additional force to its poisonous effects

That there is a form of chronic cerebellar degeneration to which alcoholics are liable has been recognised in recent times only since Romano et al [7] described 5 cases in 1940 Other reports have followed, and no less than 16 cases were reported by Chodoff et al [8] Victor et al [9] have now described the pathological findings in 11 instances, 4 of them symptomless, which came to necropsy The atrophy, which sometimes is obvious to the naked eye, is almost confined to the vermis and especially the anterior and superior parts (including the lingula, central lobule, and culmen) and so is liable to be missed unless the cerebellum is cut in the midsagittal plane All cellular layers are involved, especially the Purkinje cells, for this and other reasons Victor et al regard this as a zonal, and not just a transynaptic, degeneration Cell loss in the olives was noted in all but 2 of these cases, and occasionally the dentate nucleus showed a loss of cells They have found 11 reported cases in alcoholics with cerebellar changes comparable to those they describe

Victor et al studied 46 cases clinically In half of them the onset was rapid (in 1 case it dated from an episode when the patient was trying to avoid road traffic), in 16 it was slow, and in 7 the disorder was mild for a time and then became rapidly worse Although, in general, progression was associated with continued drinking and poor nutrition, exacerbations seemed to be related to neither in some the disorder actually worsened during a period of abstention, and occasionally accentuation of the symptoms dated from an accident or an operation Thus Victor et al find it difficult to believe that the toxic action of alcohol is the primary cause of the degeneration, but of their patients three-quarters were malnourished when they first came under observation The ataxia involved especially the legs and gait, which is in keeping with the pathological findings and the known somatotopic representation of limbs in the vermis In a few cases, however, there was incoordination of the arms and thickness of speech Occasional findings were nystagmus, ocular dysmetria, and rhythmical tremor with certain sustained postures Half the patients had an associated polyneuritis, the presence of which may mask slight cerebellar impairment Half of them had clinical evidence of liver disease, and in 14 cirrhosis was present 4 had Wernicke's encephalopathy, and a few had signs of hepatic encephalopathy Two-thirds of these patients complained of their "rubber legs" before the age of 50, the youngest patient was 31

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[4] Bricker N S Morrin P A F, Kime S W *Amer J Med* 1960, 28, 77

[5] Kleeman, C R, Hewitt, W L, Guze, L B *Medicine, Baltimore*, 1960, 39, 3

[6] Wilks, S *Med Times Gaz* 1868, 2 470

[7] Romano, J, Michael, M, Merritt, H H *Arch Neurol Psychiat* 1940 44, 1230

[8] Chodoff P, Auth, T, Torepin, H *J nerv ment Dis* 1956, 123 376

[9] Victor, M, Adams, R D, Mancall, E L *Arch Neurol* 1959, 1, 579

Victor et al place occlusion of the vertebral and basilar arteries high on the list for differential diagnosis, with multiple sclerosis as an alternative not to be forgotten—and even Wilson's disease, because rhythmical tremor when present tended to be in proximal groups of muscles Most difficulty was found in distinguishing this condition from resolving Wernicke's encephalopathy they point out, however, that in the latter the ataxia is limited to the function of stance and gait and is not manifest during individual movements of the legs

The neuropathologist will be interested in the variety of Purkinje-cell changes noted in the seemingly healthy controls, and the classifier of disease will view with interest, and perhaps criticise, the attempt of Victor et al to dispose of all known forms of cerebellar cortical degeneration in six categories

HÆMOGLOBIN MOLECULE

ONE of the triumphs of modern chemistry has been the analysis of the aminoacid sequence in insulin, for which Frederick Sanger received a Nobel prize in 1958 The hæmoglobin molecule has also attracted special attention because of its physiological importance Aminoacid sequences have been determined, and Ingram [1] discovered that the difference between normal and sickle-cell hæmoglobin was due to the difference in one single aminoacid in one of its constituent chains Ingram's work is a development of the protein analysis pioneered by Sanger

The hæmoglobin molecule, which, like other proteins, consists of polypeptide chains, is remarkable for having four ferroporphyrin groups which are thought to be attached to these polypeptide chains by histidine side-chains In human hæmoglobin the chains have been identified by their terminal aminoacids which, in adult hæmoglobin, are valyl-leucyl in one (the α-chain) and valyl-histidyl-leucyl in the other (the β-chain) In human fœtal hæmoglobin the α-chain of adult hæmoglobin is combined with a third type of chain—the γ-chain—which has glycyl as its terminal aminoacid residue Each molecule consists of four chains—two α and two β chains in adult hæmoglobin, and two α and two γ chains in fœtal hæmoglobin [2] A change in the aminoacid sequence of either the α or the β chains results in abnormal hæmoglobins [3] No variant of the γ chain has yet been reported Two abnormal hæmoglobins have been described as having no α chains Hæmoglobins H and Barts are composed only of β and γ chains respectively [4,5]

The hæmoglobin molecule is not a long fibre but a spheroid, and the polypeptide chains must, therefore, be bent in many places to fit into this shape It is here that the physicists take over to determine the shape of the polypeptide chains and thence the microstructure of the hæmoglobin molecule Indeed, if aminoacid sequence determines the way in which these polypeptide chains are bent, it might one day be possible to conclude that a certain aminoacid sequence must be present because a polypeptide chain was found to be of a given shape Vice versa, one might be able to determine the bending and cornering of a polypeptide chain in a protein molecule simply by determining the aminoacid sequence

Our knowledge of the physical structure of the hæmoglobin molecule is based on work done on horse hæmoglobin by Dr Max Perutz and his colleagues in Cambridge, and on the research carried out on the related simpler chromoprotein, myoglobin, which his colleague Dr J C Kendrew has been pursuing, using material obtained from the whale Two important communications on the three-dimensional structure of these protein molecules have been published by these workers and their collaborators from the Medical Research Council unit for molecular biology at the Cavendish Laboratory in Cambridge and the Davy-Faraday research laboratory, Royal Institution, London [6,7] Kendrew and Perutz have also addressed the Royal Institution, where they were introduced by Sir Lawrence Bragg, who is associated with the first use of X rays to determine crystal structure His object at the time was rock salt, and it must have given him satisfaction to see his technique now applied to much more complicated molecules

Unlike hæmoglobin, myoglobin does not consist of four polypeptide chains but of one only It contains 153 aminoacids and only one hæm It is an intracellular pigment which serves for the temporary storage of oxygen The form of the myoglobin molecule is spheroidal Many polypeptide chains of protein are not straight chains but are arranged in the shape of a spiral, the helix, according to a brilliant hypothesis first put forward by Pauling and Corey,[8] which has now been confirmed The α-helix arrangement, however, would still not explain the spherical form of the myoglobin molecule, and the additional bending of the spiral "staircase" has been examined by shining X rays through myoglobin crystals

The use of the X-ray-reflection technique for measuring distances between atoms in protein molecules has been made practicable by Perutz's observation that the combination of heavy atoms with such molecules produces changes in the position of reflections seen in the X-ray photograph By adding two heavy atoms, points of reference are made which allow a quantitative interpretation of the distances between the reflections According to the distance between the X-ray reflections, different structures can be determined By using 1½ Å one obtains about 20,000 reflections per myoglobin molecule, which indicates that individual atoms are being photographed With 2 Å, giving 10,000 reflections, it is possible to picture the configuration of the individual chains, and with 6 Å (400 reflections) it is possible to photograph the convolutions of the chain in the myoglobin molecule, because the distance between flexures is about 6 Å Thus, 1½ Å reveals the primary structure, 2 Å the secondary, and 6 Å the tertiary structure of the myoglobin molecule

The tertiary structure was discovered by Kendrew some years ago, when he demonstrated a peculiar worm-like model which portrayed the convolutions of the main chain in the myoglobin molecule Though the aminoacid sequence of myoglobin was quite different in the sperm-whale and the seal, the tertiary structure seemed to be very much the same in both Dr Kendrew [7] has now reported on the completion of stage II, in which the arrangement of the main chain and the position of side-chains were photographed This was no mean effort, and the interpretation of the 10,000 reflections required something like 250,000 computations The main chain turned out to have a hole in the middle and to have a helical structure of exactly the type predicted by Pauling and Corey The helices are right-handed, and of the 153 aminoacids 70% are arranged in that way, the remainder presumably forming the side-chains Eight lengths of α-helix could be differentiated, and the iron atom was seen to be attached to the main chain through a histidine side-chain The X-ray photographs were made on crystals, and on the side of the iron opposite to where it was attached to the histidine side-chain water could be seen This water is thought to take in crystals the place which in vivo is occupied by oxygen

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[1] Ingram, V M *Nature, Lond* 1956, 178, 792, *ibid* 1957, 180 326
[2] Schroeder, W A *Prog Chem org nat Prod* 1959, 17, 322
[3] Ingram V M *Brit med Bull* 1959, 15 27
[4] Jones, R T, Schroeder W A, Balog, J E, Vinograd, J H *J Amer chem Soc* 1959, 81, 3161
[5] Hunt J A, Lehmann H *Nature, Lond* 1959, 184, 872
[6] Perutz, M F, Rossmann M G, Cullis A F, Muirhead, H, Will, G, North, A C T *Nature, Lond* 1960 185, 416
[7] Kendrew, J C, Dickerson, R E, Strandberg B E, Hart, R G, Davies, D R., Phillips D C, Shore, V C. *ibid* p 422
[8] Pauling, L, Corey, R B *Proc U S nat Acad Sci* 1951, 37, 235

In the case of hæmoglobin Perutz and his team determined, first of all, where the hæm groups are placed They are arranged in two pairs, 34 and 36 Å apart By using an aperture of $5^1/_2$ Å four polypeptide chains could be identified, and there were two types of chains, each of which was present in duplicate One of the two chains resembled the myoglobin chain more than the other The two identical hæmoglobin chains seemed to be closely linked, and the amino-group end of one was very near to the carbonyl end of the other within the molecule

It is still not easy to understand why once one hæm has become oxygenated, the second hæm is oxygenated twice as fast, and the third three, and the fourth twenty times, faster The hæm groups are not close to each other, but, as Dr Perutz pointed out at the Royal Institution, the various hæms may possibly be linked by sulphydryl groups which facilitate the passage of oxygen

POLIOMYELITIS-LIKE ILLNESS

THE recovery of Coxsackie viruses, particularly those of the B group, from patients with aseptic meningitis, or "non-paralytic poliomyelitis", has often been reported, and the recovery of these viruses from the cerebrospinal fluid, taken in conjunction with the epidemiological evidence, leaves little doubt of the ætiological role of these viruses Less commonly, Coxsackie viruses of group A have been shown to have an ætiological role in aseptic meningitis But the association of Coxsackie viruses with an illness which closely resembles paralytic poliomyelitis is sufficiently unusual to merit comment

In 1952 Chumakov et al[1] in Russia observed three children with what was thought to be bulbospinal poliomyelitis, from whom they isolated a virus which they could not identify In monkeys the virus caused paralysis, with poliomyelitis-like lesions on histopathological examination of the central nervous system But the virus was antigenically distinct from poliovirus types 1, 2, and 3, and Chumakov et al understandably called it type-4 poliovirus The Russian workers did not have access to Coxsackie typing sera, but workers in the U S A and in Sweden were able to show that the Russian virus was in fact a Coxsackie virus A type 7 Coxsackie A7 viruses have been found to cause aseptic meningitis in the past, but reports of paralytic disease have been rare One such instance was described by Ranzenhofer et al[2] in the U S A in 1958, and this week we publish on p 1054 a preliminary account by Dr Grist of further isolations of Coxsackie viruses from cases of poliomyelitis-like illnesses in Scotland Of 33 patients from whom Coxsackie A7 viruses were isolated 7 had paralytic illnesses, and 1 of these died The clinical and epidemiological findings will be awaited with interest Possibly paralytic infections with Coxsackie A7 virus in people vaccinated with poliomyelitis vaccine may sometimes give a false impression that the vaccine has been inefficacious

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[1] Chumakov, M P , Voroshilova, M K Zhevandrova V I , Mironova, L L Itzelis I I Robinson I A *Probl Virol* 1956, 1, 16

[2] Ransenhofer I R Dizon F C , Lipton, M M , Steigman, A J *New Engl J Med* 1958, 259 182

W H O

THE World Health Organisation has faults as well as virtues, and some of them are reflected in the annual report of the Director General[1] The medical reader, at least, would prefer a shorter survey containing more numerical data Nevertheless its list of current projects (which makes up about half the book) is a very inspiring catalogue of genuine endeavours to make this a healthier and happier world

Malaria can be abolished, and there is hardly a country where eradication is not in progress or at any rate planned The doctors have done their part, and the responsibility for paying the bill lies with the politicians There will be more mouths to feed, but many millions more with the energy to raise their standards of living Given the will and the money, smallpox and yaws could likewise be completely suppressed, and in all these measures W H O has shown the way News of the great plagues no longer depends upon the arrival of a ship with the yellow jack in the rigging patient clerks in Geneva sort weekly returns from all over the world to warn port officers of what may be on the way Few countries cursed with trachoma have the resources for constructive research Thanks to W H O , laboratories in many lands collaborate on this problem—and with some success The report lists about 500 projects on these and many other subjects Europe, as is proper, gets less attention than those parts of the world where a man is old at 40 Almost every country receives local help in one or more fields, and all enjoy their share of travelling fellowships lasting from one month to two years

Of all the benefits of W H O these last are of outstanding value—and not only to the recipients London (and every other great centre of learning) at this moment houses men and women from all over the globe who spend their days in clinics and laboratories learning by sharing in the day-to-day work—and there is no better way A streptococcus offers much the same problems in London or Sarajevo or Casablanca (which in the eyes of W H O is in Europe) And it would warm any Londoner's heart to hear from quondam fellows in some far-off place how kindly they feel about institutions in Keppel Street or the Whitechapel Road They are the wandering scholars of today, who treasure their experiences when the big men on the committees have to refer to their diaries to remember where they were three months ago All this work of W H O is done by a staff of less than 2000 (to whom, by the way, the United Kingdom contributes the largest contingent) on a meagre income of about $16 million The rich countries subscribe more heavily, and we hope they always will

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THE next session of the General Medical Council will open on Tuesday, May 24, at 2 15 P M , when Sir DAVID CAMPBELL, the president, will deliver an address The Disciplinary Committee will sit on Wednesday, May 25, at 10 30 A M

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[1] The Work of W H O , 1959 Official Records of the World Health Organisation no 98 Obtainable from H M Stationery Office, P O box 569, London, S E 1 Pp 283 10s

Special Articles

A PROPOSED STANDARD SYSTEM OF NOMENCLATURE OF HUMAN MITOTIC CHROMOSOMES

The following statement has been drawn up by a study group, which met to formulate an agreed system of nomenclature for human chromosomes, with a view to eliminating the confusion which has arisen from the independent publication of a variety of systems by different workers

THE rapid growth of knowledge of human chromosomes in several laboratories, following advances in technical methods, has given rise to several systems by which the chromosomes are named This has led to confusion in the literature and so to the need for resolving the differences Consequently, at the suggestion of Dr C E Ford, a small study group was convened to attempt the formulation of a common system of nomenclature

The meeting was arranged, through the good offices of Dr T T Puck, to be held at Denver, in the University of Colorado, under the auspices of the Medical School The meeting of this study group was made possible by the support of the American Cancer Society, to whom grateful thanks are due For practical reasons, it was decided to keep the group as small as possible and to limit it to those human cytologists who had already published karyotypes * In addition, three counsellors were invited to join the group to guide and aid the discussions and, if necessary, to arbitrate Fortunately, the last office did not prove necessary, and it was possible by mutual agreement to arrive at a common system which has flexibility

It was agreed that the principles to be observed by the system should be simplicity and freedom, as far as possible, from ambiguity and risks of confusion, especially with other systems of nomenclature in human genetics It should also be capable of adjustment and expansion to meet the needs of new knowledge of human chromosomes The system should be agreed to by the greatest possible proportion of cytologists working in the field, but the risk that a minority may be unable to accept the system as a whole should not be allowed to delay adoption by a majority

It was agreed that the autosomes should be serially numbered 1 to 22 as nearly as possible in descending order of length, consistent with operational conveniences of identification by other criteria The sex chromosomes should continue to be referred to as X and Y, rather than by a number which would be an additional and ultimately a superfluous appellation

It was generally agreed that the 22 autosomes can be classified into seven groups, distinction between which can readily be made Within these groups further identification of individual chromosomes can in many cases be made relatively easily Within some groups, especially the group of chromosomes numbered 6–12, including also the X chromosome, the distinctions between the chromosomes are very difficult to make by presently available criteria However, lesser difficulties are encountered in separating chromosomes 6 and the X from the remainder of this group It is believed that, with very favourable preparations distinction can be made between most, if not all, chromosomes

It is proposed that the autosomes first be ordered by placing the seven groups as nearly as possible in descending order of size Within each group the chromosomes are arranged, for the most part, by size It was desired specifically to avoid the implication that the size relationships have been permanently decided in every instance, but it is hoped that the assignment of numbers will be permanently fixed In those cases where distinction is at present doubtful, final definition of each chromosome can be left until further knowledge has accrued, though an attempt is made to provide a characterisation of each These principles make it possible to draw up a conspectus of the chromosomes, a table of their quantitative characteristics and a table of the synonyms which authors have already published These are appended (tables I, II, and III)

In table II, showing the diagnostic characters of the chromosomes, three parameters are relied upon These are

(1) The length of each chromosome relative to the total length of a normal X-containing haploid set—i e, the sum of the lengths of the 22 autosomes and of the X chromosome, expressed per thousand

(2) The arm ratio of the chromosomes expressed as the length of the longer arm relative to the shorter one

(3) The centromeric index expressed as the ratio of the length of the shorter arm to the whole length of the chromosome

The two latter indices are, of course, related algebraically quite simply, but it is thought useful to present both here In some chromosomes, the additional criterion of the presence of a satellite is available (table I), but in view of the apparent morphological variation of satellites, they and their connecting strands are excluded in computing the indices

Table II shows the range of measurements determined by various workers Some of the variation expresses the uncertainty due to measurement of relatively small objects, but many of the discrepancies between different workers' observations are due to the measurement of chromosomes at different stages of mitosis and to the effect of different methods of pretreatment and preparation for microscopic study The ranges shown, therefore,

TABLE I—CONSPECTUS OF HUMAN MITOTIC CHROMOSOMES

Group 1–3	Large chromosomes with approximately median centromeres The three chromosomes are readily distinguished from each other by size and centromere position
Group 4–5	Large chromosomes with submedian centromeres The two chromosomes are difficult to distinguish, but chromosome 4 is slightly longer
Group 6–12	Medium-sized chromosomes with submedian centromeres The X chromosome resembles the longer chromosomes in this group, especially chromosome 6, from which it is difficult to distinguish. This large group is the one which presents major difficulty in identification of individual chromosomes
Group 13–15	Medium-sized chromosomes with nearly terminal centromeres (acrocentric chromosomes) Chromosome 13 has prominent satellites on the short arms Chromosome 14 has small satellites on the short arms No satellites have been detected on chromosome 15
Group 16–18	Rather short chromosomes with approximately median (in chromosome 16) or submedian centromeres
Group 19–20	Short chromosomes with approximately median centromeres
Group 21–22	Very short, acrocentric chromosomes Chromosome 21 has satellites on its short arms The Y chromosome is similar to these chromosomes

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* In contemporary publications the terms, karyotype and idiogram, have often been used indiscriminately We would recommend that the term, *karyotype*, should be applied to a systematised array of the chromosomes of a single cell prepared either by drawing or by photography, with the extension in meaning that the chromosomes of a single cell can typify the chromosomes of an individual or even a species The term, *idiogram*, would then be reserved for the diagrammatic representation of a karyotype, which may be based on measurements of the chromosomes in several or many cells

TABLE II—QUANTITATIVE CHARACTERISTICS OF THE HUMAN MITOTIC CHROMOSOMES

All measurements were made from cells of normal individuals, except those made by Fraccaro and Lindsten, which included cases of Turner s syndrom. Column A is the relative length of each chromosome, B is the arm ratio, and C the centromere index, as defined in the text

—	Tjio and Puck [6]			Chu and Giles [2]			Levan and Hsu [5]			Fraccaro and Lindsten *			Lejeune and Turpin[4] *			Buckton, Jacobs, and Harnden *			Range		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
1	90	1 1	48	90	1 1	48	85	1 1	49	82	1 1	48	87	1 1	48	83	1 1	48	82–90	1 1	48–49
2	82	1 6	39	83	1 5	40	79	1 6	38	77	1 5	40	84	1 5	40	79	1 6	38	77–84	1 5–1·6	38–40
3	70	1 2	45	72	1 2	46	69	1 2	45	65	1 2	45	67	1 2	46	63	1 2	46	63–72	1 2	45–46
4	64	2 9	26	63	2 9	26	63	2 7	27	62	2 6	28	62	2 6	25	60	2 6	28	60–64	2 6–2 9	25–28
5	58	3 2	24	58	3 2	24	59	2 6	28	60	2 4	29	57	2 4	30	57	2 4	30	57–60	2·4–3 2	24–30
X	59	1 9	34	57	2 8	38	52	1 6	38	54	1 6	38	58	2 2	32	51	1 7	37	51–59	1 6–2 8	32–38
6	55	1 7	37	56	1 8	36	56	1 7	37	54	1 6	38	56	1 7	37	56	1 6	38	54–56	1 6–1 8	36–38
7	47	1 3	43	52	1 9	35	51	1 9	35	50	1 7	37	51	1 8	36	50	1 7	37	47–52	1 3–1 9	35–43
8	44	1 5	29	46	1 7	29	48	1 6	33	47	1 7	37	48	2 4	29	46	1 5	40	44–48	1 5–2 4	29–40
9	44	1 9	40	46	2 4	38	47	1 8	36	45	2 0	33	47	1 9	35	44	2 1	32	44–47	1 8–2 4	32–40
10	43	2 4	27	45	2 3	30	45	2 0	33	45	2 6	34	45	2 6	27	44	1 9	35	43–45	1 9–2 6	27–35
11	43	2 8	34	44	2 1	32	44	2 2	31	43	2 2	31	44	1 6	39	43	1 5	40	43–44	1 5–2 8	31–40
12	42	3 1	24	43	3 1	24	42	1 7	32	43	1 7	37	42	2 8	27	42	2 1	32	42–43	1 7–3 1	24–37
13	35	8 0	11	32	9 7	10	32	5 0	16	34	4 8	17	33	6 8	14	36	4 9	17	32–36	4 8–9 7	10–17
14	32	7 3	12	34	9 5	9	37	4 0	18	35	4 4	19	32	7 0	13	34	4 3	19	32–37	4 3–9 5	9–19
15	29	10 5	9	31	11 9	8	35	4 7	17	33	4 6	22	31	10 0	9	34	3 8	22	29–35	3 8–11 9	8–22
16	32	1 8	36	27	1 6	38	30	1 4	42	31	1 4	42	29	1 4	41	33	1 4	31	27–33	1 4–1 8	31–42
17	29	2 8	26	30	2 1	33	29	2 4	30	30	1 9	35	29	3 1	23	30	1 8	36	29–30	1 8–3 1	23–36
18	24	3 8	21	25	3 8	22	25	2 6	28	27	2 5	29	26	4 2	21	27	2 4	29	24–27	2 4–4 2	21–29
19	22	1 4	41	22	1 9	34	24	1 2	40	25	1 3	43	22	1 4	42	26	1 2	45	22–26	1 2–1·9	34–45
20	21	1 3	44	19	1 3	44	21	1 2	40	23	1 3	43	20	1 2	43	25	1 2	46	19–25	1 2–1 3	40–46
21	18	3 7	21	15	6 8	13	13	2 5	28	19	2 5	29	15	2 3	31	20	2 5	29	13–20	2 3–6 8	13–31
22	17	3 3	23	12	6 0	14	16	2 0	33	17	2 3	30	13	4 0	20	18	2 7	27	12–18	2 0–6·0	14–33
Y	19	∞	0	11	∞	0	18	4 9	17	22	2 9	26	18	∞	0	18	4 9	17	11–22	2 9–∞	0–26

* Unpublished data

represent the maxima and minima of the means found by different workers using different techniques However, within any one worker's observations, the variations are not so broad

Reference should be made to two other matters of *nomenclature In the first place, it is considered that no* separate nomenclature for the groups is needed It is considered that any group to which it may be necessary to refer will be a sequence of those designated by Arabic numerals Hence, any chromosome group may be referred to by the Arabic numerals of the extreme chromosomes of the group, joined together by a hyphen —e g , the group of the three longest chromosomes would be Group 1–3 This scheme has the merit of great flexibility For instance, chromosomes X and 6 may be separated from the Group 6–12 whenever they can be distinguished

Secondly, there is the problem raised by the abnormal chromosomes which are being encountered in the more recent studies Their nomenclature was discussed without a definite conclusion being reached Broadly, it was agreed, however, that any symbol used should avoid incorporating a specific interpretation which was not reasonably established It was suggested that arbitrary symbols, prefixed by a designation of the laboratory of origin, should usually be assigned to the abnormal chromosome

In this connection, two further requisites for coordination of research were discussed One is the storage of documentation for reference, perhaps in a central depository, additional to what it may be possible to publish The other is the desirability that cultures be preserved, by the satisfactory methods now used, so that they are available for reference, comparison, and exchange

Some consideration was also given to the desirability of using a uniform system for presenting karyotypes and idiograms, but recognising that individual variation in taste is involved, rigidity of design was thought undesirable However, it was recommended that the chromosomes should be arranged in numerical order, with the sex chromosomes near to but separated from the autosomes they resemble It is desirable that similar ones be grouped together with their centromeres aligned

It is recognised that choice between the different possible schemes of nomenclature is arbitrary, but that uniformity for ease of reference is essential Hence, individual preferences have been subordinated to the

TABLE III—SYNONYMY OF CHROMOSOMES AS PUBLISHED BY VARIOUS WORKERS

New chromosome number	Tjio and Puck [6]	Chu and Giles [2]	Levan and Hsu [5]	Ford, Jacobs and Lajtha [3]	Böök, Fraccaro, and Lindsten [1]	Lejeune, Turpin, and Gautier [4]
1	1	1	1	1	1	G1
2	2	2	2	2	2	G2
3	3	3	3	3	3	G3
4	4	4	4	4	4	G4
5	5	5	5	5	5	G5
6	6	6	6	6*	6	M1
7	7	7	7	(8)	7	M2
8	8	8	8	(9)	8	Md1
9	9	9	9	(11)	9	M3
10	10	10	10	10	10	Md2
11	11	11	11	(12)	11	M4
12	12	12	12	(13)	12	Md3
13	18	14	20	14	14	T1
14	19	15	18	15	15	T2
15	20	13	19	16	13	T3
16	13	17	15	19	16	C1
17	14	16	13	17	17	P1
18	15	18	14	18	18	P2
19	16	19	16	20	19	C2
20	17	20	17	21	20	C3
21	21	21	22	22	21	Vh
22	22	22	21	23	22	Vs
X	X	X	X	?(7)	X	X
Y	Y	Y	Y	Y	Y	Y

* In the published idiogram the chromosomes of group 6–12 (including X) were indicated by discontinuous lines and left unnumbered owing to the uncertainty of discrimination at that time For the purpose of this table, these chromosomes have been assigned the numbers shown in parentheses, in serial order of length

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1 Böök, J A , Fraccaro, M , Lindsten, J *Acta pædiat* 1959 48, 453
2 Chu, E H Y , Giles, N H *Amer J hum Genet* 1959, 11, 63
3 Ford, C E , Jacobs, P A , Lajtha, L *Nature, Lond* 1958, 181, 1565
4 Lejeune, J , Turpin, R , Gautier, M *Ann Génét* 1959, 2, 41
5 Levan A., Hsu, T C *Hereditas*, 1959, 45, 665
6 Tjio, J H , Puck, T T *Proc Nat Acad Sci* 1958, 44, 1229

common good in reaching this agreement This human chromosomes study group therefore agrees to use this notation and recommends that any who prefer to use any other scheme should, at the same time, also refer to the Standard System here proposed

We are well aware of the wide interest in the work of this study group and realise that this meeting is merely a preliminary to a larger meeting It is believed that two needs have to be met in this respect One is for seminars and workshops at which workers in the field may exchange information, such seminars are best arranged regionally The second need, which may come later, is for international conferences, and we believe that congresses and other organisations whose interests include human genetics, should promote such meetings

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Points of View

THE PRESS, THE PATIENT, AND THE HOSPITAL DOCTOR

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PEOPLE have always interested themselves in each other's medical and surgical adventures The growth of popular means of communication has fostered this interest, and spread it to general hospital and health matters as well as to rare and peculiar diseases A distinguished or notorious patient has always been " news ", and sooner or later his story will be bound to get into newspapers and on to the air The new element is the contemporaneous detail which modern methods encourage and provide The facts must come hour by hour from the bedside For doctors and hospitals not to recognise and to make allowance for this is to invite difficulty and disturbance

The medical and nursing staff require peace of mind, freedom from personal molestation, and a quiet atmosphere in which to work It is sensible to consider in advance how best to protect them Reporters and editors have their own point of view, which like all professional viewpoints leads to methods and to behaviour difficult for the rest of the community fully to understand Looked at from the outside what they demand is the whole story in all its details at the earliest moment, if possible before anyone else hears it, and better still to the exclusion of anyone else At the worst, if they cannot scoop an exclusive story it must on no account be scooped by another paper Even with the most detailed story the reporter suspects that something important is being withheld He has a technique for starting conversations which is almost impossible to parry, and he is adept at building a story even when his victim is uncommunicative. His knowledge of human beings has taught him the worst—gold or vanity will turn most keys

When the Press is regarded and treated as an intruder, the reaction is fierce the attack is launched with no holds barred, and with artifice worthy of some better purpose This is when reporters and cameramen disguise themselves and climb the fire-escapes Possible informers are molested in person and by telephone Any titbit of news is elaborated, rumour and fancy are tricked out as fact, concern with accuracy dissolves News of a kind is printed, for the public is entitled to news Nothing else matters The doctor and the hospital have lost their peace

The patient or the relatives are in worse case They cannot hide or escape, and to their natural anxieties are added the pestering of the newsmen They can secure a limited protection National newspapers are prepared to pay to make contracts, the main purpose of which is information, with exclusive rights as an important secondary consideration There is probably no form of contract that will compel relatives or patients to tell everything that they know, but they can agree only to talk to the paper's accredited representative The losing papers will accept defeat of this kind and retreat discomfited Where any such contract has been signed, the hospital and its staff should know of it although they are certainly not bound by its terms Some doctors are angry and refuse to treat patients who are party to such contracts If undesirable publicity is likely to result there is justification for such an attitude The arrangement should be discussed in a friendly spirit, when everything will depend on the patient's discretion

Some lessons can be learned from recent experience at Saint Bartholomew's Hospital in the case of the Siamese twins The publicity problem was simplified because of the nature of the case Antenatal X-rays produced the diagnosis, so that there was plenty of time to make plans The immediate need was absolute secrecy, and by the loyalty of the hospital staff of all grades and by the common sense and discretion of the parents, the babies were delivered, remained for a month at Queen Charlotte's Maternity Hospital, and were moved to Saint Bartholomew's without comment This gave the parents a period of peace in which to accommodate themselves to their remarkable situation Intrusion into their privacy would have been intolerable But once such an unusual event as this is the subject of rumour the Press is bound quite soon to find out who and where the patients are The race to be the first on the scene is on The lure of scooping the news and the fear of being scooped leads inevitably to ill-mannered behaviour The hue and cry which lasted two days should not have occurred A factual statement should have been prepared giving the medical details for release as soon as there was the slightest suspicion of Press interest Such a statement should be as full as possible and should include an approximate forecast of the nature and the timing of treatment It should, of course, not be made, nor need it be signed, by any of the doctors concerned It should come from one of the administrative officers, and it should be sent to the Press agencies, not to any one newspaper

The agencies and individual reporters should be told that any reasonable questions will be submitted to the doctors and will be answered unless there is a good reason against this All the staff concerned should agree not to hold any individual conversations with reporters, who do accept the idea that the hospital is giving out useful information but that it is being channelled through one hospital officer to the agencies Reporters will fight for some exclusive detail for a while but a pattern of behaviour can be built up quickly which, if the hospital cooperates, gives the Press confidence and saves its reporters time and energy An appetite for detail can be assuaged by serving a surfeit

Periodic progress bulletins were sent to the agencies The Press interest was measured by the amount of space devoted to the case and the number of telephone inquiries The announcement of details was timed to some extent to meet demand

The parents did not wish to know the exact day or time of the operation, nor did the hospital want an invasion by reporters It was therefore agreed that this important piece of information should be withheld With the exercise of some ingenuity, and again helped by the loyal silence of those directly concerned, the long operation was almost completed before the Press got wind of it The announcement was to be made on the day after the operation, when the fate of the twins could be more clearly known A plan had, however, been made to release a statement, should it appear that any news had reached the Press The objects of this were to forestall a scoop and to ensure accuracy Once more the plan partly failed One newspaper telephoned the parents a little time before the hospital to report that the operation was complete The official statement was immediately released The next day a long account followed, giving many medical details, and an assessment of the prognosis and including the names of the more senior medical staff concerned With this it would have been sensible to send appropriate photographs Clearly the Press regarded the episode as of the greatest public interest The surgeon became the target for camera marksmanship for some days after the operation—an aggravating state of affairs which could have been prevented had it been accepted as proper practice for photographs to be taken by the agencies or released with the news A freely offered photograph for general distribution is less likely to be published than one secured specially and by stealth While public interest remained acute, daily bulletins were issued The actual Press reports were studied, and when some flight of fancy appeared about plans or details the true statement was included in the next bulletin There were no disputes and no denials, but reporters saw that serious inaccuracies would be shown up and acted accordingly

As time passed, interest waned and bulletins were more widely spaced The hospital promised, and kept its promise, that any important change would be revealed to the Press agencies and that due notice would be given of the date of discharge Surveying the course of this case the exercise of forethought and attention to detail seem to have been worth while At no time did publicity matters get out of hand

Some morals may be drawn and lessons learned from this experience It is of the first importance in these days that such an unusual case should be recognised as of legitimate public interest Preparation must therefore be made as to how the Press is to be handled A consistent, agreed, and cooperative policy can lead to the establishment of confidence and mutual respect between all the parties concerned Information should be available for reporters to the limit of what is seemly Professional anonymity cannot be maintained unless the whole of the Press agrees to such a policy Without this agreement members of the staff concerned are best safeguarded by the release of some information about what part they play, and availability of photographs would save them from being hunted

Conference

LIVER DISEASE

A MEETING of the International Association for the Study of the Liver was held at the Royal Free Hospital, London, on April 25 and 26 under the presidency of Prof SHEILA SHERLOCK

Bilirubin Metabolism

Dr I M ARIAS (New York) had studied bilirubin excretion in normal and clinically jaundiced (Gunn) rats He emphasised that conjugation of bilirubin in the liver was a different process from its excretion into the bile The Gunn rat, for instance, could excrete injected conjugated bilirubin but not the unconjugated form, here the defect was in conjugation The normal animal could excrete both forms In contrast, after treatment with norethandrolone ('Nilevar') both the Gunn and the normal rat failed to excrete conjugated bilirubin, showing that norethandrolone interfered, not with conjugation, but with the excretory process

Dr J CAROLI (Paris) reported extensive histochemical studies on the liver and spleen of a patient with pigmentary hyperbilirubinæmia (Dubin-Johnson-Sprinz syndrome) He believed that the black pigment in the spleen was an abnormal adrenochrome (melanin) He also noted that a secondary rise in bromsulphalein level in the serum after intravenous injection was diagnostic of this condition Dr S BRANDSTAETTER (Haifa) found this disease fairly common among young male Jews of Persian origin He had been unable to detect melanin in the spleen in two instances

Prof M MASUDA (Tokyo) reported the presence of "free" bilirubin only in the serum of the fœtus and the newborn This could easily pass the blood/brain barrier and so reach the brain It was significant in the ætiology of neonatal jaundice

Dr R WILLIAMS and Dr B H BILLING (London) confirmed the fall in serum-bilirubin levels in patients with hepatitis given steroid therapy The decrease was steep in the first twenty-four hours, and the shape of the serum-bilirubin curve then fell exponentially There was no change in the survival of erythrocytes after steroids, nor could the fall be accounted for by alterations in urinary or fæcal pigment excretion Dr W H J **Summerskill** (Mayo Clinic) reported similar results in patients with obstruction to major bileducts, and wondered whether steroids altered the solubility of bilirubin in the tissues Dr **Arias** thought this unlikely He had given steroids to one patient with jaundice due to carcinoma of the pancreas who also had multiple lipomas Serial biopsies showed less bilirubin in the lipomas after steroid therapy

Changes in Obstructive Jaundice

Prof T **Kitani** (Osaka) had found by electron microscopy underdevelopment or absence of microvilli lining the bile canaliculi in the human fœtus He had also shown in obstructive jaundice in adults that there was a communication between the liver cells linking the microvilli with the sinusoids Dr **Hans Popper** (New York) had noted disappearance of microvilli in extrahepatic biliary obstruction, " cholangiolitic " hepatitis, and drug jaundice Norethandrolone produced stunting and irregularity of the villi, whereas chlorpromazine had no such effect Cholestasis was independent of inflammatory changes in the portal zones He concluded that there was no certain method of distinguishing extrahepatic from intrahepatic obstructive jaundice Prof G **Dominici** and Dr F **Orlandi** (Perugia) had noticed dilatation of the endoplasmic reticulum spaces in obstructive jaundice They also could not distinguish histologically between extrahepatic and intrahepatic cholestasis

Veno-occlusive Disease

Prof K R **Hill** (London) described the world distribution of veno-occlusive disease of the hepatic venules It was due to poisoning with monocrotaline—a member of the pyrrolizidine group of alkaloids He had produced lesions in the hepatic venules of rats given monocrotaline, and this substance had also caused changes in tissue cultures of liver cells

Toxic Changes

Prof H **Kalk** (Kassel) reported eight cases of poisoning with trichlorphenol, an insecticide The liver remained enlarged and the thymol-turbidity test positive, but the most remarkable change was the gross pigmentation of the liver cells, continuing in one case for four and a half years after exposure There was no cirrhosis Dr T C **Chalmers** (Boston) had noted increased pigmentation in the livers of alcoholics after the fat had disappeared Dr M **Royer** and Dr B **Noir** (Buenos Aires) found that cortisone diminished ferritin fixation in the liver

Syndrome Following Virus Hepatitis

Dr S J M **Goulston** (Sydney) described a series of young patients with malaise, nausea, and hepatic tenderness persisting after acute virus hepatitis Hepatic biopsy showed cellular infiltration in the portal zones with no disturbance of architecture Steroid therapy led to portal zone scars but was not always successful The picture differed from that of active, " juvenile " " lupoid " hepatitis, for lupus-erythematosus cells were not found, endocrine changes were not seen, other organs were not involved, and serum γ-globulin was not increased Dr J **De Groote** (Louvain) had seen similar cases and believed that cure was possible even after three years' ill-health Prof P N **Wahi** (Agra) believed that when such a condition smouldered on for a long time the end-result was cirrhosis

Persistent Jaundice with Cirrhosis

Dr A E **Read** and Prof C V **Harrison** (London) described forty-five patients (eleven men and thirty-four women) with cirrhosis and jaundice lasting longer than three months Forty were less than forty years old, a third gave a previous history of hepatitis, and in two-thirds the onset was insidious The many associated conditions included nephritis, rheumatic fever, pulmonary infiltration, Hashimoto's thyroiditis, and disseminated lupus erythematosus Serum-γ-globulin levels were very high Microscopic examination showed an active cirrhotic lesion with cellular infiltration with plasma cells and lymphocytes Steroid therapy resulted in increased well-being, control of associated lesions, and return of the menses Complications of therapy included excessive weight gain and sepsis, especially of the skin Relapse might follow cessation of steroid therapy Patients survived for about five years after diagnosis, but ten patients in fact were alive five years afterwards

Acute Hepatitis

Dr R A **King** and Dr E R **Cullinan** (London) had followed up cases of acute hepatitis in the Forces in the late war and had found twenty-seven instances of definite cirrhosis Twenty-four of these were of the serum variety, and only three were preceded by acute infective hepatitis

Treatment of Cirrhosis

Dr **Peter Dykes** (Birmingham) had treated thirteen cirrhotic patients with fluid retention by intravenous salt-poor human albumin, giving 50 g daily until the serum colloid osmotic pressure was normal Sometimes as much as 1500 g was needed Three patients lost their predominant œdema, and five of ten their ascites Those responding showed an expansion of their plasma volumes In successful cases serum-albumin levels were maintained over long periods by infusions of albumin 50 g every one to two weeks Increased well-being was conspicuous, and four patients were leading active lives Dr **Perry J Culver** (Boston) noted that if the serum-albumin level rose by more than 0 5 g per 100 g albumin infused the result was usually satisfactory

Dr W V **McDermott**, Jr (Boston), had treated intractable ascites in cirrhotics by " double " porta-caval anastomosis, both ends of the portal vein being joined separately to the inferior vena cava Of seventeen patients fifteen survived the operation, and fourteen were relieved of their ascites, subsequently episodes of hepatic precoma developed in three

Dr C L **Gantt** (Chicago) had treated sixteen cirrhotic patients with ascites by spironolactone, an aldosterone antagonist Seven had a diuresis, and failures often later responded when chlorothiazide was added One patient unsuccessfully treated with spironolactone had a normal urinary aldosterone excretion, and necropsy showed a blocked portal vein Dr R **Morrison** and Dr T C **Chalmers** (Boston) had noted hyponatræmia after the combined use of spironolactone and chlorothiazide, the addition of prednisone increased water loss and prevented this complication Dr S Shaldon and Miss J McLaren (London) had added mannitol as an osmotic diuretic Of fourteen patients so treated ten lost their ascites, five of these no longer needed spironolactone, but in five ascites reaccumulated and spironolactone therapy was being continued Dr Summerskill believed that 1400 mg spironolactone was sometimes needed for a few days before diuresis ensued In four patients uræmia followed diuretic therapy with spironolactone and chlorothiazide, and this was related to loss of tonicity of body-fluids, more sodium than water being excreted

Hepatic Blood-flow

Dr J Caesar, Dr L Guevara, and Dr L Chiandussi (London) had measured hepatic blood-flow by the extraction of ^{131}I-labelled denatured human albumin from the blood The mean flow in healthy subjects was 1576 ml per minute, compared with 852 ml per minute in cirrhotics There was evidence that part of the blood flowing through the liver in cirrhosis was not perfusing the sinusoids Dr A Neumayr (Vienna) had measured hepatic blood-flow before and after inflation of a Senstaken œsophageal compression tube He estimated the flow through œsophageal varices to be 300 to 500 ml per minute

Portacaval Anastomosis

Dr Brandstaetter believed that a rise in the glutamine content of the cerebrospinal fluid after oral ammonium chloride might indicate a tendency to neuropsychiatric complications after a portacaval anastomosis This might be useful in the selection of patients

Blood-pyruvate

Dr J M Walshe (Cambridge) and Dr H Orrego (Santiago) reported a failure of lipoic acid to influence blood-pyruvate levels after glucose loading in cirrhotic patients Of sixteen patients with Wilson's disease ten had abnormal pyruvate levels after glucose

Public Health

Infectious Diseases in England and Wales

Disease	Week ended April				
	2	9	16	23	30*
Diphtheria	1	3	3	7	3
Dysentery	2465	2547	1745	1228	1199
Encephalitis					
Infective	2	3	2	4	3
Postinfectious	2	6	1	3	4
Food-poisoning	273	229	131	130	137
Measles, excluding rubella	2466	2143	2124	2487	2273
Meningococcal infection	24	24	12	22	20
Ophthalmia neonatorum	28	25	22	23	16
Paratyphoid fever	3	3	1		4
Pneumonia, primary or influenzal	441	465	297	362	342
Poliomyelitis					
Paralytic	3	2	2	4	4
Non-paralytic	2		2	2	1
Puerperal pyrexia	144	192	159	156	169
Scarlet fever	1054	1171	795	708	520
Smallpox					
Tuberculosis					
Respiratory	430	467	376	378	458
Meninges and C N S	5	1	3	7	6
Other	52	38	47	50	64
Typhoid fever	1			3	2
Whooping cough	943	916	694	815	994

*Not including late returns

Medicine and the Law

Homosexual Tendencies Not Cruelty

A wife petitioned for divorce on the ground of her husband's alleged cruelty The parties had been married in 1943, when the husband was 33 and the wife 29 There were two children of the marriage The wife's complaint was that since 1945 the husband had desired to dress up and behave like a woman

In 1945 she had discovered women's clothing in her husband's suitcase He had explained that by saying that in his youth he had dressed up as a woman In 1955, when the husband thought that she was visiting her parents, she had returned to the matrimonial home to find that he had women's clothes, cosmetics, and powders in the bedroom When challenged, he had cried and asked for her help The wife had suffered severe shock, had a complete nervous breakdown, and from June until September, 1955, was a patient in a sanatorium, suffering from agitated depression for which she received electrical treatment The husband refused to have treatment In April, 1958, the wife, coming home early, found her husband in the bedroom dressed like a woman He told her that he wanted to be a woman and live with another man Thereafter they lived at arm's length until December, 1958, when the wife left

Her petition was undefended, but the Special Commissioner dismissed it on the ground that cruelty had not been made out The wife appealed, and the Court of Appeal dismissed her appeal

Lord Justice Willmer said that the doctor who had attended the wife in 1955 had said that she was at first suffering from agitated depression but that by October, 1955, she had sufficiently recovered to give a lucid account of what had happened

He had been asked " Are you prepared to say that she had been greatly affected in her health ?" and had replied " At that time she suffered from very severe shock She felt he was obsessive and tried to conceal from herself the full extent of his perversion But as she realised its full extent she became more and more shattered She was disgusted with this thing " Another doctor who had attended her later said that a recurrence of the 1955 breakdown was a distinct possibility

The decisive thing in the present case was the secretive nature of the husband's activities He had done his best to conceal his tendencies and had only indulged them when he could reasonably suppose that he would not be discovered Had he openly paraded his tendencies, knowing that they would distress his wife, cruelty would have been established But he concealed them, and that made it impossible to impute to him any intent to injure his wife Nor could the inference to injure her be drawn from his refusal to have treatment The real cause of the wife's distress was not his abnormal behaviour but the fact that she had little sexual attraction for him Treatment would not have remedied that matter Therefore the decision of the Special Commissioner that cruelty had not been made out was right, and the wife's appeal would be dismissed Lord Justice Harman and Lord Justice Sellers delivered concurring judgments

Bohnel *v* Bohnel *Court of Appeal* Sellers, Willmer and Harman *L JJ* May 2, 1960 Counsel and solicitors Roger Ormrod, Q C , and George Dobry (Pennington & Son)

Norman Primost
Barrister-at Law

In England Now

A Running Commentary by Peripatetic Correspondents

We who live in cities but cherish memories of the countryside may still be made to feel that we are a part of Nature. Now and then, a thunderstorm will burst upon our heads or a sudden wind will topple the idols of masculine elegance and tumble the artificial edifices of haute coiffure. At such times there is a sense of clinging to the Earth with prehensile toes, of peering through the coarse fronds of unkempt hair, face to face with the old gods. In these elemental moments we are back to the wild mating of falcons and the "long, long thoughts" of youth. Paradoxically, the turbulence of natural forces then compels us to reconsider our destiny and we catch a glimpse of subjects worthy of the great essayists. It can happen in a twinkling—whenever there is an eddy in the orderly flow of Time: hiding from the rain in a doorway, a speck of dust in the eye, the pause before a sneeze. Any event can do it, so long as it is too unruly for the powers of puny Man to withstand or to control.

It was, as a matter of fact, while I waited for the electric toaster that I hit upon a short description of the new Chinese bicycle. The peculiar idiosyncrasy of this machine is that a canvas fan is mounted on the handlebars and linked by a chain to the gear system. When the cyclist is delayed by a demoniac head-wind in his hasty ride to work, the fan rotates and so assists him in his struggle with the pedals. The stronger the wind, the faster turns the fan and the faster runs the bicycle, so we are told.

Now I own with humility that the principle of this device raises physical—almost metaphysical—problems and doubts which I am unable to resolve. For example one might argue that the thing would only work if the losses due to drag and friction were less than the torque transmitted to the wheels. If this were so, then surely it should work even in still air? One can see in the mind's eye how the rider, first pushing his conical hat more firmly down on his head and hitching up his trousers, might run a few yards with the cycle to get up speed and then leap on—with a whirr and a rattle, round spins the blue canvas propeller, faster and faster as the diabolical mechanism acts back on itself, the hitherto inconvenient back-thrust of the air now lending added impetus to the vis-a-tergo. With ever-increasing velocity and legs flying round like a centrifuge we see him at last, disappearing from view across the Paichong plains.

What if some coldblooded thermodynamician sneeringly points out a fallacy, refers slightingly perhaps to the conservation of energy, and proves that the invention has in fact only added to the immemorial burden of the coolie? It may be so, but if there is greatness in defying the thunderstorm, in being engulfed by a sneeze, then how much more greatness there must be in flouting the very Laws of Nature! What Science forbids, Poetry decrees. We should be grateful that so much of the old China still survives.

* * *

Insulated by a devoted nursing staff from my colleagues, the telephone, and the patients, I had much time to read and to reflect. Omar Khayyam was a rediscovered delight. From that I moved to the more mundane medical journals and, too introspective to read the clinical articles, thumbed over to the doings of the Royal Colleges. The names of those recently admitted as members or fellows were vaguely familiar—Khan and Mahmood, El Sherrawy and Rifkind, Budagolu and Abdul Rahman. I had met them before. There they were—there in the Rubaiyat—Jamshyd and Kaijobad, Zal and Rustum, Hatim and Mahmud.

> Into this Universe, and *Why* not knowing
> Nor *Whence*, like Water willy-nilly flowing,
> And out of it, as Wind along the Waste,
> I know not *Whither*, willy nilly blowing.

But how did they manage in Glasgow? Had they an interpreter? The fearful garrulous harridan of a Glasgow mother, protecting her speechless infant at the pædiatric clinical, a "Vessel of a more ungainly make", explaining with a simplicity and clarity that left each candidate speechless: "Tae let understaun, Doactor, the wean's been hinging back and furrit for nigh a foartnicht. Gae toutie in fact."

* * *

There is no doubt that we are not as tough as our forebears. On the right of our house is a chicken farm run by a frail-looking old lady of 79. Her chickens and eggs are the best for miles around because the chickens run free in the orchards and are well fed. She is blind in one eye, nearly stone deaf, and has survived two major operations. She gets up at 5 A.M. and goes to bed at 9 P.M., and rules her daughter and the chickens with a rod of iron.

To gain her attention so as to order eggs or a chicken you have to toll a large bell on her back porch. She does not hear the bell but her four dogs tell her when it is rung. If she is carrying a 56 lb. sack of meal on her back she will put it down gently and then deal with your order. Once I rashly offered to carry a large bale of hay for her. Seventy yards later she took it off me without ceremony and continued the journey holding the bale on her shoulder with one hand whilst she selected the right key to the shed from a key-ring the size of a saucer which was slung round her hips on a chain. She hasn't changed at all in the ten years we have known her.

Next door on the other side is a couple who have just collected Granny to live with them. Granny is 87 and hitherto has looked after herself and has refused to be moved. But last year she started to forget things, so after a stand-up fight she was moved next door, but she cannot remain idle. At the moment she is washing down the walls (which are spotless) and she has insisted on their redecoration. She sits on the top of a ladder and when she has finished all she can reach she yells downstairs to be moved along a few feet. They were very worried in case she fell, but as she is cottage-loaf in shape her centre of gravity is very low when sitting down, and anyway she's enjoying herself and there is comparative peace. Soon the house will be completely redecorated. They are spinning it out as much as they can until the Seville oranges come in, but they have removed most of the empty jam-jars because they remember the last time she made jam and couldn't, or wouldn't, stop. After that there will be the rhubarb and then the gooseberries, but despite these plans I notice that they wear a slightly hunted look next door. Even television is a mixed blessing because now Granny has had her cataracts removed she's determined to see the programmes to the bitter end. Being old, she needs little sleep—and there are still the walls of the pantry to finish.

* * *

"I would have thought that in the circumstances the solution was eminently simple."

"What exactly do you mean by *I would have thought*? Do you, for example, wish to convey that you have given this problem no previous attention, but that had you done so the solution would have stuck out like an organ-stop? Or do you wish to tell me that there is no problem, that any half-wit other than myself would be able to see that the logical answer was so and so? Perhaps you are concealing something? Maybe it is the fact that you have given this problem a great deal of thought and that you have fixed ideas on its solution. Perhaps this is one of your pet tub-thumps. But being a well-mannered chap you wish to clothe your convictions with an air of educated nonchalance. Perhaps you haven't the slightest idea what it was I said. Perhaps you are unsure of yourself. I would have thought that a serious self-analysis on these lines should constitute a major contribution to your thinking."

* * *

ELMS IN APRIL

Green snow suspended in mid-air,
The new, soft leaves float around trees
Whose trunks, dressed still in thick, stained coats
Could surely not claim kin with these
Fantastic, frivolous and fair
Ethereal motes of greenery.
Yet those boles raise sap from deep roots,
Earth's distilled riches flow unseen,
Are filtered through to meet the sun.
The sunlight into life has run,
Age knows no loss of dignity
When the tall trees spin silken green.

Letters to the Editor

EXPIRED-AIR RESUSCITATION

SIR,—I was interested in the article of April 2 by Professor Woolmer and his colleagues From the evidence presented by them, and by previous workers in this field, there seems no doubt of the efficacy of this method of resuscitation The following incident, however, has raised a doubt in my mind

A short time ago I was called to see a lightly built man of average height, aged 45, who had collapsed at his work I arrived about 30 minutes after the collapse Holger-Nielsen artificial respiration was being efficiently performed by a competent medical attendant and had been for 20 minutes After a brief examination I considered the victim was probably dead Nevertheless, I cleared a small amount of vomitus from the mouth, covered the lips with a handkerchief and performed mouth-to-mouth artificial respiration Having previously seen Dr Safar's film and used a manikin, I was as competent as anyone was likely to be The chest rose and fell excellently, but after three or four breaths a very large quantity of vomitus was extruded from the mouth This was again cleared and a further attempt was made Things went quite well for a few minutes and the medical attendant then took over from me, continuing for about five minutes During this time I made further examination and decided that beyond doubt the victim was dead The artificial respiration was stopped I noticed the abdomen was slightly distended and I gently pressed the epigastrium with a resultant reflux of a further pint of vomitus

The past history of this man, as obtained from his superiors, suggested chronic renal disease and hypertension with a history of attacks of unconsciousness He also had an enormous appetite and would eat vast quantities of food—a pound of cheese and loaf of bread at a sitting were apparently not at all unusual

The postmortem report showed that the man was chronically anæmic, and that he had bilateral polycystic disease of the kidneys The cause of death was acute congestive heart-failure The stomach contained mucus only and no vomitus was present in the bronchial tree Thus, mouth-to-mouth artificial respiration had effectively emptied the stomach

Several questions arise

Was this regurgitation simply due to displacement of stomach contents by air, or was it due to strong excursions of the diaphragm on an overfull flaccid stomach, or a combination of these?

Would the use of an airway have altered this situation in any way?

If life is present, is the tone of the cardia, poor though it may be, still enough to prevent entry of air?

Experimental evidence on the efficacy of expired-air resuscitation in people with full stomachs is lacking—quite rightly so since the danger is so great Patients who have paralytic diseases requiring prolonged positive pressure breathing usually have intratracheal airways inserted

Before advocating the general adoption of expired-air resuscitation, the question of regurgitation from the stomach must be clarified

I should like to thank Dr R A Goodbody, consultant pathologist, *Southampton Group Hospitals, for permission to give some details* of his postmortem report

Esso Refinery,
Fawley
Southampton

G MATTHEWS

A HAZARD OF PHOTOCOPYING

SIR,—As an industrial medical officer my attention was directed to an annotation in a business management journal which described a method of rendering paper more translucent for the purpose of photocopying by the dyeline process

This annotation described how documents for photocopying should be wiped over with a solution consisting of trichlorethylene *B P* 2 parts, tricresyl phosphate 1 part, acetone *B P C* $^1/_8$ part It stated that this solution could be obtained at any chemist's shop

The article described how the documents so treated will dry rapidly, thus enabling them to be photocopied There was no warning about the use of this material, in spite of the fact that trichlorethylene is not only an anæsthetic but has been described as producing mental changes due to prolonged absorption, and is a drug of addiction

The second ingredient, tricresyl phosphate, is not only equally toxic (if not more so than trichlorethylene) but is also a cumulative poison attacking the nervous system, and, what is most important, it is absorbed through the skin

It is highly probable that in many offices and drawing offices where there is a need to photocopy letters, plans, and blueprints, photocopying has become a minor industry It may well be that it is often carried out by young women who are probably ignorant of the hazards of this process It is equally probable that, in an attempt to speed up the operation, the treated paper is held in front of a radiator or fire to hasten the drying process, and it is quite certain that the method described should be adopted only when steps are taken to ensure that no fume or vapour escapes into the atmosphere and none of the solution comes into contact with the operator's hands

In view of the particular nature of the effects of tricresyl phosphate, it is most improbable that young women engaged on this work would be correctly diagnosed and more than likely they would go off sick after a period of some months' exposure, with a condition which might be mistaken, for example, for poliomyelitis

During my investigation into this matter, I was also informed that an alternative method was to use a mixture composed of equal parts of carbon tetrachloride and castor oil This seems an equally suspect process in view of the anæsthetic effects of carbon tetrachloride, and the same chronic effects on the kidneys and liver

With the increasing adoption on office premises of mechanised equipment and technical processing of the kind described above, much of this work is probably carried out in the least suitable places—namely, an ill-ventilated basement

At the present time there is, as your readers will know, a Bill before Parliament to safeguard the health, safety, and welfare of office workers The control of working conditions in offices such as described, becomes not only desirable but probably lifesaving

London, N 6

J C GRAHAM

HUMAN RELATIONS IN OBSTETRIC PRACTICE

SIR,—Doctor's wives who read your journal will be grateful to Professor Morris for his timely and inspiring address and for Dr Abraham's comment on it (April 30)

I am impressed by the fact that such an address should be needed That such a state of affairs exists, and needs pointing out to doctors, is surely a reflection on the state of the healing art today My own experience has been fortunate, in that I had my first baby in one of London's best obstetric units, and my second one in ideal conditions at home Nevertheless I have seen and heard enough to convince me that the "sausage machine" approach to midwifery exists in the attitude of some of the nursing staff concerned with hospital confinements At this most vulnerable period of a woman's life it only takes a small amount of impersonal and brusque handling to produce a considerable reaction, I am sure that Dr Abraham's type of patient is not rare

One does not expect doctors and nurses to be perfect, and although ideally Dr Abraham may be right in advocating extensive teaching of dynamic psychology to those concerned, in the meantime is it not a matter of simple humanity to be able to remember that parturition is much less commonplace for the mother than for the experienced midwife?

London, S W 19 CYNTHIA JACKSON

SIR,—It is refreshing to see the note introduced by Professor Morris' article Is it not time that all our hospital beds should be reserved for human people, members of families and of communities? For far too long have we been concerned with bed occupancy and the cost of an empty bed, but might not recovery be a little quicker (and dare I suggest more complete?) if the patients were treated generally in a more humanitarian fashion?

Is it really necessary for the pace to be so fast that no-one can be certain whether or not Mrs X is definitely on tomorrow's list until after visiting hours? Wouldn't it be more reasonable to allow "someone" time to explain that "you may wake up with a tube running into your arm and another into your nose" and the reasons for the likely duration of these measures Many people undergoing surgery have no idea where the scar will be Surely a basic instruction to all who deal with people should be explain to the patient, *in terms he will understand*, what you are going to do and what he may expect as a result, and allow him an opportunity to ask questions if he wishes

We talk about mental health and positive health, is it not time that we tried to estimate how much mental discomfort we as a profession may be responsible for?

I would add that these comments relate to the many frustrations I felt during the years I worked in hospitals because, for various reasons, I found myself unable to carry out these ideals

Hadleigh,
Essex. DAPHNE SASIENI

MERIT AWARDS

SIR,—The letter of "Junior Medical Officer" (April 9) on the subject of merit awards prompted me to buy a copy of the Royal Commission's report The figures he correctly quotes on the distribution of awards by specialty show all too well that a prophet is not without honour save in his own country Over 55% of physicians receive awards 51% of surgeons 41% of obstetricians of psychiatrists but 14% receive recognition and anæsthetists are dismissed with a contemptuous 13% This discrepancy is commented upon by the Commission itself (p 82) and I understand that the leaders of the anæsthetists suggested to the Commission that the distribution of awards was rather low for this specialty

Now these two apparently despised branches have one thing in common in each case the value of the service rendered to medicine and to the community has greatly increased in recent years I cannot speak on the international reputation of British psychiatry but it is no exaggeration to say that, in the eyes of the world, British anæsthesia is unique it is well ahead of any other country not only in the ability of the leaders, but also in its overall level Postgraduates come from all countries to study anæsthesia here the diplomas of the Faculty of Anæsthetists are the most prized in the world and anæsthetic services established abroad are modelled on the English pattern

It would be an insult to suggest that the Awards Committee may be unaware of the efflorescence of this branch of medicine Since this cannot be so, then it is all the more important that the appearance of deliberate refusal of adequate recognition be rigorously eschewed As justice has to be seen to be done as well as be done, so the very appearance of injustice must be avoided most particularly when some of the near-Star-Chamber qualities of the administering body render it potentially suspect

IN SOMNO PAUPERTAS

TREATMENT OF SALICYLATE POISONING

SIR,—In your annotation of April 23 you state "Continuous washing of the stomach is perhaps advisable, as salicylate may possibly be excreted into the stomach or be regurgitated from the small intestine during vomiting" This may perhaps possibly be as indecisive a remark as one can make, but aspirin poisoning is a common and dangerous hazard and deserves careful thought

Professors Goodman and Gilman [1] are more forthright when they state "It (salicylate) is not secreted in the gastric juice even at high plasma levels" They also maintain when discussing salicylate poisoning that the gastrointestinal symptoms, including vomiting, can occur without the appearance of salicylate in the gastric juice, and give references

If this is incorrect, there are, as you suggest, obvious important therapeutic implications You do not, however, give any reference in support of your statement, and before we discard other expert opinion, and particularly before we subject our patients, who are often toddlers, to repeated lavage, which is not without danger in a struggling vomiting baby, it is desirable that we should be allowed to examine the evidence on which you base your remark

I feel rather strongly on this point partly because my resident was involved in the inquest you mention, where this point among others was raised, but mainly because your annotation might be regarded in some quarters as an authoritative expression of present opinion If it were, and as some cases of aspirin poisoning will die whatever is done, further residents in the future may be criticised for not giving "continuous" lavage, which at the moment I personally regard as at best unnecessary I am, however, open to correction

Manor Hospital,
Walsall J M GARVIE

*** Our editorials seldom aim to review a subject exhaustively, and the one to which Dr Garvie refers was not intended to deal comprehensively with the many opinions on the treatment of salicylate poisoning We quoted Professor Webster's view but did not mean to imply that other opinions should be discounted Many may feel, however, that continuous washing of the stomach is still advisable in the early stage of poisoning when salicylates would be expected to be present in the stomach and intestine Goodman and Gilman's observations do not seem to weaken this first principle of treatment We assure Dr Garvie and his resident that we intended no criticism of the treatment in this particular case, for, as Dr Garvie observes, some patients poisoned by salicylates will die whatever is done —ED L

SIR,—Your annotation described the various methods which have been directed towards correction of the electrolytes in this condition No mention was made, however, of the deaths which frequently occur due to respiratory failure, regurgitation of vomit, or exhaustion These dangers are not always fully appreciated but their importance and prevention have been discussed by Freier et al [2]

In the case which they described the boy had an initial blood-salicylate level of 66 mg per 100 ml He was intubated following an injection of *d*-tubocurarine chloride and controlled ventilation was maintained for 12 hours After cessation of controlled ventilation the breathing was normal in rate and depth and there was no recurrence of tetanic spasms

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[1] Goodman, L S, Gilman, A The Pharmacological Basis of Therapeutics p 291 New York, 1956

[2] Freier, S, Neal B W, Nisbet, H I A, Rees, G J, Wilson, F *Brit med J* 1957, i, 1333

Intubation with a cuffed tube ensures that hypoxia is prevented and the obstruction of the relaxed tongue is bypassed Furthermore, regurgitation of vomit is prevented so that tube-feeding may be instituted with safety

Curarisation and controlled ventilation reduce the hyperactivity of the voluntary muscles and thereby reduce the probability of further disturbances in the electrolyte balance Reduction of this hyperactivity lowers the hyperpyrexia so that death from exhaustion in small children is less likely to occur

I believe, therefore, that treatment should be directed primarily towards restoration of the airway in those patients who are suffering from severe salicylate intoxication When this has been achieved, attempts may be made to restore the normal electrolyte balance in the blood It is difficult in some cases to decide when this method of treatment should be instituted, but once the patient begins to hyperventilate, the necessary anæsthetic equipment and drugs required for intubation and controlled ventilation should be at the bedside

Celander and Haglund[3] have described three cases which were treated on similar lines by controlled ventilation through a tracheostome

Southmead Hospital,
Bristol

FRANK WILSON

BLOOD-VOLUME IN ELDERLY ANÆMIC PATIENTS FOLLOWING BLOOD-TRANSFUSIONS

SIR,—I read with interest Dr Andersen's article of April 2

These studies conform with other work which suggests that the infusion of blood-plasma does not always or even regularly result in the anticipated expansion of the plasma-volume Dr Andersen has suggested that this phenomenon can be explained by "simple physicochemical forces which displace fluid and proteins from the circulating blood into the extracellular spaces spaces" thereby regulating the total blood-volume and the plasma-volume

However, recent studies in man and animals deny the simple explanation offered by Dr Andersen Dogs were transfused firstly with autologous plasma which had been obtained from the same animals previously and held in the frozen state, and secondly with non-autologous or homologous plasma derived from other animals of the same species[4,5] A dramatic difference was noted in the response of the same dogs to autologous and non-autologous plasma An excellent expansion closely approximating to the anticipated value was obtained in almost all those dogs receiving autologous plasma When, however, the same dogs received non-autologous plasma the expansion was frequently poor and in some cases an actual contraction of the plasma-volume was noted to occur in less than one hour following the infusion of plasma Accompanying these transfusions (of non-autologous plasma) extensive urticaria was often noted A fall in blood-pressure sometimes accompanied the cutaneous reaction The evidence suggested that these reactions were due to a histamine release resulting from the infusion of plasma-proteins of a non-autologous donor More recently we have duplicated these studies in volunteers[6,7] Ten healthy individuals received approximately 500 ml of autologous plasma which was held in the frozen state for at least a week before reinfusion The increase in the plasma-volume was equal to 83% of the anticipated value When fifteen healthy volunteers were infused with the same quantity of non-autologous plasma the mean retention, as determined by radioactive iodinated serum-albumin, was only 18% Six of the fifteen developed urticaria during the infusion and four developed systemic reactions including headache, fever, chills, and nasal stuffiness In general, a poor expansion of the plasma-volume was encountered in those individuals having severe reactions No reactions were encountered in the recipients of autologous plasma In all cases, the plasma-volume was determined one hour after infusion of the plasma

It appears therefore that while some adjustment of plasma volume after transfusion is undoubtedly due to simple loss of plasma-protein from the circulation, a more important factor in clinical transfusion is the occurrence of plasma incompatibility leading to an increased capillary permeability

Montreal General Hospital

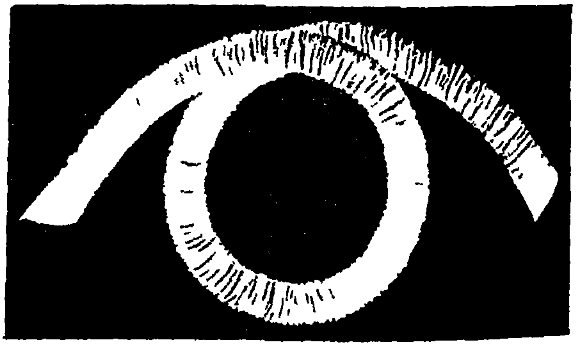
J L HUTCHISON

A TERYLENE ARTERIAL PROSTHESIS FOR USE IN THE LOWER LIMBS

SIR,—The plastic fibre 'Terylene' was first developed in Britain by Imperial Chemical Industries, but it is also made, under licence, in the United States of America where it is known as 'Dacron', recently this material has been used in America to construct arterial prostheses of various types In the crimped forms these artificial grafts have proved highly successful for arterial grafting in the lower limbs

Julian et al[1] have demonstrated, by animal work and by clinical trial, the suitability of a crimped tube of taffeta-weave dacron as an arterial substitute in the lower limbs Our own experience, using the same material in some 54 cases over the past year, has amply supported Julian's observations and we have come to regard this as the form of artificial artery of choice in the lower limbs

The textile division of the Imperial Chemical Industries of Great Britain have now evolved a pure terylene arterial substitute (see figure) which seems to conform well to Julian's recommendations, to distinguish this from the American product it is proposed to refer to it as "terylene arterial prosthesis", although we freely acknowledge our debt to our American colleagues for perfecting this form of plastic artery The principal reason for developing a British terylene arterial substitute has been to reduce substantially the cost as compared with the imported dacron product



The terylene arterial prosthesis has the possible advantage over the dacron counterpart that the lateral flanges characteristic of the latter have been abolished Our impression is that the terylene graft is even more satisfactory than the dacron graft with regard to the ease with which the fabric is made blood-proof by pre-clotting

The terylene arterial graft shows no appreciable tendency to fray when it is cut, and the crimping employed appears to give good protection against buckling when it is angulated It is supplied sterilised by gamma-rays, but of course it can be boiled or autoclaved in addition, the manufacturers cleanse the material of any chemical contaminant before it is supplied 8 mm has been adopted as the standard diameter of this tubing because experience has shown that this will meet nearly all requirements in the lower limb, other diameters are available

We have now used the terylene arterial prosthesis in 37

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3 Celander, O, Haglund G *Acta anesth scand* 1958, 2, 123
4 Bliss, J Q, Johns, D G, Burgen, A S V *Circulation Res* 1959, 17, 79
5 Bliss, J Q, Walker J D *Canad J Biochem Physiol* 1959, 37, 371
6 Freedman S O, Bliss, J Q, Hutchison, J L, Burgen, A S V *J Allergy*, 1960, 31 134
7 Hutchison J L, Freedman, S O, Richards B A, Burgen, A S V *J Lab clin Med* (in the press)

1 Julian, O C, Deterling, R A, Dye W S, Bhonslay, S, Grove, W J, Belio M L, Javid, J *Arch Surg* 1959, 78, 260

patients requiring a femoropopliteal arterial grafting procedure and the results have been observed for up to six months This limited experience has shown that the terylene grafts possess all the excellent qualities of the American counterpart and should be capable of yielding long-term results equal to those reported by Julian. It is the purpose of this communication to draw attention to the availability of the British product, but it is our belief that the proper assessment of the procedures for which it is likely to be used will require some years

Bifurcated abdominal grafts of similar material will be available shortly

British-made terylene arterial prostheses may be obtained from Messrs John Bell & Croyden, who also supply the imported American dacron arterial prostheses

Royal Victoria Infirmary,
Newcastle upon Tyne.
Hammersmith Hospital,
London, W 12

D J TIBBS
PETER MARTIN

MONDAY-TO-FRIDAY WARDS

SIR,—In your issue of April 30, Miss Simpson suggests the possibility of Monday-to-Friday wards as a feature of hospital planning of the future. In the geriatric unit in this hospital, we have over the past few months been experimenting along these lines with certain of the longer-stay rehabilitation patients, as a logical extension of the principle of intermittent hospital care, of which the "six weeks in, six weeks out" scheme pioneered by Dr John De Largy at Langthorne Hospital, E 11, is, a well-known example We hope to report our experiences shortly, but in addition to easing the nursing load we feel it to be of value to this group of patients in particular, because it maintains their links with their homes and encourages the relatives to consider themselves part of a team responsible for the planning of long-term care of patients who might otherwise become depressing problems to themselves and their families, and indeed to the hospital staff who will ultimately have to care for them

Ystrad Mynach Hospital,
Hengoed, Glamorgan

MORAG L INSLEY

PAROMOMYCIN IN SHIGELLA AND SALMONELLA INFECTIONS

SIR,—I found the article of April 30 by Dr Coles and his colleagues extremely interesting I feel that if they had included more cases in which a chronic carrier state developed, refractory to other forms of treatment, due to salmonella infection, then the evaluation of paromomycin activity would have been easier As we all know, this type of case is the one which is most likely to block valuable hospital cots and beds

My experience in Fazakerley Hospital, Liverpool, using a different form of therapy, may be of interest. Under the guidance of Dr A. B Christie, I treated 10 children, between the ages of 18 months and 5 years, in whom the chronic carrier state due to *Salmonella typhimurium*, refractory to other forms of treatment, was well established with a combination of oral oxytetracycline (terramycin) (15 mg per lb body-weight daily) and 'Enpac' (3–4 g. daily) for five days 9 of these patients were cured (three negative consecutive rectal swabs) In the 10th case two negative swabs were obtained and then the organism returned. These patients had all been previously treated with oral oxytetracycline and most had also received a course of oral streptomycin and sulphaguanidine.

A patient of 70 infected with *S newport* was in hospital for nine months because of his chronic carrier state and the fact that he owned, worked in, and lived over a cafe. He was treated with a similar regime, and "cure" was obtained on two occasions using a criteria of six consecutive negative rectal swabs, but the organism always recurred on further testing He finally sold his business and was then discharged from hospital.

I consider that this treatment is rational because the enpac supplies resistant lactobacilli to replace the bowel flora disrupted by oxytetracycline

St. Vincent's Hospital,
Dublin.

J S DOYLE

FLUORIDATION

SIR,—The replies of the medical officers of health to Dr Dobbs seem to show that we have to fight not only for pure water but for common sense in public-health affairs Can *all* our public-health experts approve of imposing a general, indiscriminate, permanent increase in the intake of a well-known poison and believe that the infliction of worry, indignation, and stress upon innumerable middle-aged people and invalids is the duty of the medical profession?

This insistence on coercion, and on a method which involves arousing the maximum possible public hostility, cannot arise from a sincere concern for the children's teeth, it is clear that the fluoridation campaign is being used, by those few who really know what they are doing, to break down the principles of consent and of individual care and treatment, which are absolutely fundamental to medicine and to public confidence in the medical profession

Huddersfield.

WINIFRED M SYKES
Secretary,
National Pure Water Association

HÆMORRHOIDS

SIR,—Your leading article of Feb 20 on the treatment of hæmorrhoids and the correspondence which followed prompt us to record the results we have been obtaining with a comparatively new product Although you recommend only injection or surgical removal, many milder cases do not warrant or the patient does not accept such treatment Even in severe cases where hæmorrhoidectomy is contemplated, the patient's suffering must still be relieved during the waiting period

Patients with hæmorrhoids of varying severity were given a supply of 'Proctosedyl' (Roussel) suppositories and/or ointment (each suppository and each gramme of ointment contains 5 mg hydrocortisone, 10 mg framycetin sulphate, and 5 mg cinchocaine) They were instructed to apply the ointment and insert a suppository morning and evening

The results in 35 cases are summarised as follows

1st degree hæmorrhoids complete relief 14, helped 2, failed 1 (17)
2nd degree hæmorrhoids complete relief 10, helped 1, failed 1 (12)
3rd degree hæmorrhoids complete relief 4, helped 1, failed 1 (6)

Only 3 out of 35 patients received no benefit at all, but 32 received benefit of varying degrees, and 80% obtained complete relief

Protoscopy was carried out at the first and subsequent visits to determine progress All possible serious underlying diseases were also carefully excluded The patients were followed for periods of several months and those who did not return for final assessment were excluded

In fissure-in-ano results were also excellent, 4 out of 5 patients obtaining complete relief, but in the symptomatic treatment of pruritus ani, pruritus vulvæ, and vulvitis results were disappointing

Bitterne,
Southampton.

W L KERR
T E S STOWELL
T WADE WEST
J F MULLAN

SIR,—I have now treated approximately 50 patients with the preparation 'Alcos-Anal', mentioned by Dr Mustard (April 9), reserving it mainly for pregnant women with symptoms of hæmorrhoids, including slight bleeding

Over 90% of patients stated that there was considerable relief of discomfort and even of pain, and that bleeding, when it occurred, was less than before treatment No patient required injection or operation treatment after delivery, although at the initial postnatal visit, 2 patients looked as though they would need hæmorrhoidectomy Three months later, the hæmorrhoids had considerably decreased in size with continued use of this preparation, which contains the sodium salts of unsaturated fatty acids of cod-liver oil

The main disadvantage of this therapy is an unpleasant stinging sensation which lasts for about ten minutes after the ointment, or the pessary, has been introduced into the anus

London, W 1 ELLIOT PHILIPP

BRONCHOGRAPHY

SIR,—I read with interest the article of March 5 by Dr Smith and his colleagues I cannot agree with their contention that " A trained assistant is necessary to position and support the patient normally a physiotherapist " I use a much simpler method which gives excellent filling

The patient, after insertion of the tracheal catheter, is placed on the X-ray table which is tilted 5°–10°, feet downwards The patient reclines at an angle of about 45° with the side to be filled lowermost and the head well supported on a couple of pillows The patient hyperventilates half-a-dozen times and then holds the breath in full expiration The dye is injected down the catheter as rapidly as possible (16–18 ml suffices for each side in an average adult) and the patient is then instructed to breathe in normally Films are taken immediately, erect or supine as desired With a little experience, this technique gives consistently uniform filling of all lobes on the side being investigated

Incidentally, this method is readily adaptable to bronchography under general anæsthesia This is performed with a short-acting relaxant, and the dye is " pushed out " into the bronchi by manipulation of the anæsthetist's bag, which at the same time keeps the patient oxygenated

I do not claim originality for this method, but merely wish to draw the attention of Dr Smith and his colleagues and others interested to a much quicker and simpler method of performing bronchography both under local and general anæsthesia

Hobart,
Tasmania JOHN BLOOMFIELD

IMMUNE TOLERANCE IN MOTHER AND FŒTUS

SIR,—It is strange that Dr Galton (Feb 27) should state that no account has been taken of the antigenic action of the placenta

Medawar [1] as far as I am aware first discussed this problem I pointed out [2] the extraordinary inconsistencies that inevitably arise when syncytiotrophoblast is considered of fœtal origin, and suggested, as a reasoned solution, that the problem really did not exist since the tissue concerned may well be maternal of granulosa-cell origin Since then discussion has ranged wide and speculation almost equalled that of the schoolmen who argued how many angels could be present on the head of a pin Dr Park (April 16), as he indeed points out, recently discussed this problem, but he does not mention that of the three solutions he posed, he found none satisfactory, the last of the three was that the trophoblast differed antigenically from the rest of the fœtus of which it is said to be part Unlike Dr Galton, he finds difficulty in accepting this solution

This placental tissue, according to various contenders, is primitive, or highly specialised, antigenically simple, or complicated, ectoderm, mesoderm, entoderm, or all rolled into one as " protoderm " It produces the hormones of the pituitary, ovary, adrenal, and endometrium of the mare, and thus contains within itself both the conductor and players of the hormone orchestra The nuclei are haploid without Barr chromatin bodies or polyploid with them It is a cancer and it is not, and when without a doubt it is a cancer as chorionepithelioma it invades another individual, the mother, but not the fœtus of which it is part Derived from the fœtus, it has an existence apart from it, as in the hydatidiform mole The theory of recapitulation (which states that an individual in its embryonic stages recapitulates the life of the species), although somewhat rusty these days, is turned upside down And so on! All these difficulties cease to exist if the syncytiotrophoblast arises from granulosa cells and its function is to protect fœtus and mother from each other antigenically

Should Dr Galton succeed in demonstrating that syncytiotrophoblast nuclei are haploid the hypothesis I have suggested would not be invalidated unless the granulosa cells surrounding the ovum did not have haploid nuclei To add to the current speculation, if these latter cells have haploid nuclei they could be parthenogenetic twins (or rather multiplets) of the fertilised ovum

Public Health Offices,
Ilford I GORDON

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[1] Medawar, P B *Quart J micr Sci* 1948, 89, 239
[2] Gordon I *Lancet*, 1949, i, 807

A PORTABLE FREE-FIELD AUDIOMETER

SIR,—The exchange of views on the free-field audiometer (April 16) raises problems in audiometry which are worth discussing in detail

Mr Ashton restated some well-known acoustic principles concerning audiometry when earphones are used and contrasted this with free-field audiometry when poor acoustics can reduce the accuracy of the measurement The use of earphones makes the measurements independent of the sound-reflecting quality of the room but *not* independent of other conditions and qualities of the room In fact, *conditions under which tests are frequently carried out* are one of the major sources of error in audiometry You may have a good machine in a perfectly acoustically treated room, but if it is an unventilated small *cubicle* in which both the subject (mainly when a child or elderly person) *and the examiner* suffer acute discomfort, the result will be frequently a false one If you add to it an inadequately trained audiometrician (unfortunately still a very frequent occurrence) who does not use a standardised procedure, the result will be wide of the mark This still happens again and again *It is not so much the machine* or lack of acoustic treatment of walls which leads audiometry into disrepute, but lack of suitable conditions and thorough training of audiometricians (mainly in testing children) This is a pity, because undoubtedly pure-tone threshold audiometry is still the best single test which informs us about the physiological condition of the hearing apparatus

It is high time it was realised that audiometric tests cannot be carried out satisfactorily in small, miserable, unventilated cubicles A cubicle or any unfriendly poky little room is entirely unsatisfactory for this important subjective hearing test

Physical standards for the machines have been worked out but we still lack standardisation of satisfactory conditions for the test, and even standardisation of technique

Audiometry in children requires a good-sized, pleasant, and comfortable room in which play audiometry, using conditioning methods, can be carried out I have found the Denes-Reed free-field audiometer particularly useful in preparing a small child for full threshold audiometry

The child is first conditioned, in free field, with an interesting sound Then the play continues with pure notes, with the help of the free-field audiometer At this stage I introduce a transitional step Initially, many children may be reluctant to wear large earphones, so I use a single earphone, unattached to a wire, which has a transistorised oscillator incorporated in it This produces a moderately loud single note when a spring is pressed, and the earphone is slowly moved towards the child's ear until it rests on the auricle Probably he will now tolerate the large earphones more readily and can be transferred from free-field testing to more accurate threshold audiometry

In addition it must be remembered that earphones are designed for adults Frequently they are too big and cumbersome for the head of the small child No manufacturer of audiometers has yet thought to provide earphones and headbands designed primarily for children Inaccurately fitting earphones will invalidate results obtained from the best machine under perfect acoustic conditions

Harrow L FISCH

NOT TOO BIG

SIR,—From your editorial (April 30) on the psychiatric hospitals of the future I note that a bed complement of 300 is suggested to keep the hospital sufficiently small It would be interesting to know the size of the population for which it is intended to cater In the Manchester region, fully comprehensive psychiatric departments in a general-hospital setting are being built up, and I think we are discovering—somewhat to our amazement—how few beds are in fact needed if the department is properly organised

My own department (which is in a general hospital) has 99 beds and serves a catchment area of some 254,000 Though at this stage I cannot give actual figures, I can safely say that, at a conservative estimate, it is coping with at least 85% of all inpatients This assumes that the beds are not blocked by subnormal patients, that there is an active and cooperative geriatric department in the hospital group, and that so-called community mental health services are fully organised If these provisos are met, I am left with the strong impression, on the basis of actual experience, that fewer psychiatric beds are needed than might be thought necessary on a-priori grounds

Blackburn. MAURICE SILVERMAN

PREVENTION OF SERUM HEPATITIS

SIR,—In your annotation of April 16, you say that "donors with a previous history of jaundice are unacceptable" This can hardly be correct, partly because jaundice may be due to proven cholelithiasis and partly because of the studies of Matthes and Riderer [1] They studied the frequency of inoculation hepatitis in recipients who had received blood from donors with hepatitis at different times before the bleeding They came to the following results

Of 85 transfusions with blood from donors who had suffered from hepatitis six years or more before the bleeding 3 (3 6%) gave rise to hepatitis in the recipient Of 30 transfusions for which the corresponding interval was 3–5 years 2 recipients (6 3%) developed hepatitis, and for the intervals 1–2 years, 7–12 months, and 3–6 months the corresponding figures were 24 and 2 (7 8%), 19 and 2 (10 2%), and 3 and 2 (66 7%) The proportion of hepatitis among recipients receiving blood from donors *without* a history of hepatitis was found to be 4 2%—i e, of the same order as for donors with hepatitis 6 years or more before the bleeding As everyone who is responsible for obtaining sufficient blood for a hospital will know, it is hard to get sufficient donors, and it therefore seems to make things unnecessarily difficult to exclude all donors with previous jaundice, when well-documented investigations clearly show that donors with hepatitis more than 6 years back are not more dangerous than donors without a history of hepatitis

Concerning the interesting paper of Bang et al,[2] referred to in your annotation, it is important to remember that of the donors tested for S G O T 23 2% had values above 40 Wroblewski units, 12 5% had 50–100 units, and 2 1% above 100 units If S G O T should function as a screen test for eliminating donors it would therefore be quite unrealistic to use 40 Wrobleswki units as the limit, and if 100 units is to be used as a limit the whole matter seems rather problematic In my opinion the results of Bang et al show that S G O T is not usable as a screen test for eliminating hepatitis carriers among donors

Svendborg, Denmark TORBEN K WITH

AN EASIER ALPHABET

SIR,—So many issues (and a few dubious arguments) have emerged in the discussion of redundancy that some ends are bound to be left untied May I however make an attempt to show how some of them may be woven into a coherent pattern?

There seems to have been some confusion between the concepts of "redundancy" and of "noise" If we imagine an ideally simplified alphabet and then add to each of the letters a *different* "curl, ball or spike", we are making the letters more specific, since this is not strictly necessary, the added information is redundant If on the other hand we add *the same* ornament to each and every letter we are making the letters more complex but not more specific. The ornament is worse than useless, for it obscures the differences between letters—it is "noise" Noise, which is *irrelevant* information, must be distinguished from redundancy, which is *superfluous relevant* information, the former is always noxious, the latter always potentially protective

Now in the card-sorting experiment it was shown that when the cards differed in colour, shape, and size, but were sorted only according to colour, certain illiterates were unable to ignore the shape and size differences and would work at a rate corresponding not to 1 bit/card but to 3 bits/card From this it was very reasonably inferred that the irrelevant information concerning shape and size was retarding their performance It would be more consistent to go on to say that performance was retarded because the brain was *unable to exclude noise* than to incriminate redundancy

According to the usual electronic analogy, an efficient brain has an intrinsically high signal/noise ratio and is therefore able to pick out a signal from a background of noise Returning to the idea of a "noisy" alphabet, above, it will be clear that a reader who recognises that the same ornament is present in all the letters has taken the first step towards ignoring it His brain must be able to discriminate, and become selectively accommodated to, any invariant characteristic of all the letters A brain which lacks the ability to detect the "highest common factor", and becomes unresponsive to it in this way, will have to continue handling each letter whole instead of "recognising" it by a minimal number of cues My feeling is that Dr Pugmire's card-sorting experiment (April 23) has really revealed a low signal/noise ratio for visual perception in certain illiterates and that noise rather than redundancy is the evil of which we should seek to rid our language, not only its alphabet, but at all levels It is precisely when the communication system has a low signal/noise ratio that redundancy in the signal has its greatest protective value, hence my remark "It may be that redundancy in the script is only protective where the defect lies in the perception and recognition of printed symbols, rather than in the comprehension of words"

Perhaps it should be made more explicit that just as the addition of extra specific detail to letters is a redundancy which protects primarily against the misidentification of *letters*, so the presence of seemingly superfluous letters in a word is mainly a guard against misidentification of the *word*, similarly for the presence of "superfluous" words in a sentence, sentences in a paragraph, and so on So long as the extra matter is relevant, a certain amount of repetitiousness is valuable, especially is this so in printed language, where no information can be conveyed, nor can the attention of the audience be ensured, by the devices of intonation, facial expression, and gesture, which are so important a part of speech.

Finally, I would assure Dr Jarrett (April 23) that the word "cough" does illustrate the general principle that "redundancy protects" Consider the misprints arising from error in any one of the three letters "ugh" The only two words with which "cough" could be confounded are "couch" and "couth" If, however, the word were normally spelt "cof", misprinting of the letter "f" could result in no fewer than ten distinct words The "ugh" spelling reduces the ambiguity caused by a misprinted letter That this ambiguity is not merely an academic abstraction may be seen from the devastating effect of misprinting "cough" in the famous *sloca* which I will proceed to relate

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[1] Matthes M, Riderer U *Dtsch med Wschr* 1956, 81 1914 *Germ med Mon* 1957, 2, 107

[2] *J Amer med Ass* 1959, 171, 2303

"It wasn't the couch that carried him off
But the coffin they carried him off in"

The distinction between redundancy and noise does not only bear upon the relatively abstruse problems of language statistics but also upon the intelligent management of every communication task It might be summed up, perhaps, in the advice "Repeat yourself if necessary, but stick to the point"

London, W 1 H B G THOMAS

THE COMPREHENSIVE HANDBOOK ON PRESCRIBING

SIR,—A new handbook with this title has been issued this week to all practitioners on the National Health Service list It is a most sumptuous edition There is as far as I could see nothing new in it not already covered by previous publications The outdated 14-pin binder is not the easiest to handle, but obviously no expense has been spared It is provided with a pocket for the *National Formulary*, which might be useful if it could enter it

We are told in the first paragraph of the green section that we are "expected to exercise reasonable care in avoiding waste of public funds" Were ever so many before told to do this in so expensive a manner?

Thornton Heath B DE BURCA

RESISTANT ASCITES TREATED BY COMBINED DIURETIC THERAPY

SIR,—The interesting observations of Dr Shaldon and his colleagues (March 19) on the additive diuretic effect of mannitol administered in combination with spironolactone (SC-9420, 'Aldactone') for the treatment of resistant ascites may have failed to adequately emphasise the contribution of the aldosterone antagonist in promoting loss of ascitic fluid

Our experience[1] in eight patients with cirrhosis and refractory ascites treated with spironolactone after appropriate control periods showed a remarkable response in every case The clinical response in terms of loss of fluid was not apparent until the drug had been administered for periods of 2–5 days, and then was stepwise and progressive for several days thereafter Early experience using total daily dosages of 400 mg indicated this dosage was often inadequate, and the optimal dosage among our patients was 600–800 mg daily

The addition of mannitol on the second day of treatment with spironolactone may coincide with the beginning of the clinical response to this drug and the effects of any additional therapy would then be inseparable

In our observations[2] on four patients, the addition of mannitol (2 litres 10% solution administered intravenously) to spironolactone, after the latter had been given continuously for 5 days using a total daily dosage of 800 mg, was not followed by an increase in the volume or sodium content of the urine above that found during the administration of aldactone alone

Our studies indicate that the resistance to diuretics, encountered in patients with cirrhosis and ascites, is due in a large part, if not entirely, to hyperaldosteronism and that adequate treatment antagonising the effects of aldosterone will, by itself, induce diuresis The disadvantages of administering mannitol intravenously would additionally appear to lessen its usefulness in the long-term management of patients with cirrhosis and resistant ascites

Mayo Clinic,
Rochester

B F CLOWDUS
J A HIGGINS
J W ROSEVEAR
W H J SUMMERSKILL

THE PERSONAL DOCTOR

SIR,—The vexed questions whether the general practitioner should be a "personal doctor" or whether he should be one of a large specialising group practice, whether he should work from his house or from a central clinic, or whether he should even exist at all, affords much thought for speculation and argument, but the fact remains that we are committed to a general-practitioner service and it behoves us to seek ways to make it as efficient as possible To my mind, paradoxically enough, it is the specialists who can be of most help

The value and status of the G P will never be at its best, or anywhere near it, until the specialists see that the hospital service and the G P service work as one When the G P has facilities for diagnostic aids on direct application and has at his disposal G P hospital beds, as well as the use of a minor-operation theatre and ample opportunities for clinical assistantships in outpatient departments, then, and only then, can he give of his best and take a reasonable part in the Health Service of this country At the moment, in most parts of this country he is denied all these things

Even those who have higher degrees or those who show proof of special experience in a specialty (e g, hold a diploma) can find no outlet for this experience, and it seems that most consultants are determined that they never shall

Many reasons for this attitude spring to mind but heated discussion of them would lead nowhere, and I am sure in the long run that, if only the specialists would open up their closed shop, they themselves would also benefit, because they would be really seeing only those cases that needed a specialist's opinion The public would also benefit and it could well be that the cost of the Health Service might be lowered

London, S W 11 IAN SAMUEL

PREVENTION AND TREATMENT OF BEDSORES

SIR,—I feel that Dr Pathy (March 12) has rightly stressed that, even at an early stage of a pressure sore, necrosis has extended to fat and muscle, and that this emphasises the greater importance of turning a patient than of local applications

It has been suggested[1] that the devitalised atrophic tissues of an elderly patient may actually suffer damage when rubbed with spirit or other preparations

With this in mind, a number of bed-fast, and mostly incontinent, patients in a geriatric ward had their pressure areas and sores routinely treated with the following silicone preparation, in the form of an ærosol spray

Aluminium dihydroxyallantoinate	0 5% w/v
Cetyl pyridinium chloride	0 1% w/v
Terpineol	1 0% w/v
Silicone fluid	ad 100%

The aluminium dihydroxyallantoinate and cetyl pyridinium chloride are suspended as finally micronised powders

In addition to the water-repellent and protective properties of the silicone compounds, the spray combines the astringent and bacteriostatic action of aluminium with the healing properties of allantoin Cetyl pyridinium chloride possesses bactericidal properties, and terpineol is a pleasant-smelling antiseptic

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[1] Clowdus, B F, Higgins, J A, Rosevear, J W, Summerskill, W H J *Proc Mayo Clin* 1960 35, 97

[2] Clowdus, B F, Higgins, J A, Rosevear, J W, Summerskill, W H J Unpublished data

[1] Bateman, F J A *Brit med J* 1956, i, 554

The original formula contained liquid paraffin, but as this prolonged the drying time it was omitted

Only a momentary pressure on the aerosol spray button was required to deliver a film of silicone fluid on to the patient's skin Unless fouled, the skin was washed infrequently, and the patient's position changed as often as possible

It was felt that the incidence of bedsores had been reduced The nursing staff was enthusiastic about this method of treatment, for æsthetic and time-saving reasons Compared with the old methods of rubbing with spirit, &c, the patients were spared unnecessary discomfort, and the simplicity of the aerosol method would suggest its suitability for use in the home-nursing of the elderly, in colostomy hygiene, and the prevention and treatment of napkin rash

Chorlton-cum-Hardy,
Manchester

H H D KELLY

ORAL HYPOGLYCÆMIC AGENTS

SIR,—Dr Henry Dolger's experiences with chlorpropamide have been so unfortunate and so different from those of others on this side of the Atlantic, including our own, that one is tempted to doubt whether the high incidence of jaundice reported by him in his letter of April 30 can be entirely attributed to the use of this drug

In the small series of cases reported by us[1] there was no instance of jaundice, and this complication has not been observed in any of the much larger number of patients at present receiving chlorpropamide in our diabetic clinic The total incidence of jaundice in patients receiving chlorpropamide therapy in the United Kingdom is 0 02%

Even more surprising are his remarks on hypoglycæmia which would not appear to be a manifestation of idiosyncrasy and which we have encountered only rarely and almost always in a mild form using the regime described in our article

In some early trials of chlorpropamide[2] there was a significant incidence of toxic effects, now recognised as being due to overdosage, the high incidence of severe hypoglycæmia and jaundice reported by Dr Dolger suggests the possibility that the use of this drug in more than therapeutic doses may have been the responsible factor

Before condemning chlorpropamide as a significant cause of jaundice, Dr Dolger should present some good reasons for regarding it as being a propter rather than possibly just a post hoc manifestation, Graham[3] reported a number of cases of jaundice occurring in a diabetic clinic long before the days of the oral hypoglycæmic drugs, the only common therapeutic agent being insulin

No doubt Dr Dolger will be publishing the detailed findings in the two cases which developed jaundice on chlorpropamide in a daily dose of 250 mg, in the meanwhile it will be unwise to draw conclusions from his remarks

The Diabetic Clinic,
King's College Hospital,
London, S E 5

W G OAKLEY
D JACKSON

PALLIATION OF MALIGNANT STRICTURE OF THE ŒSOPHAGUS

SIR,—I agree with Mr Moghissi (March 26) that the Mousseau-Barbin tube is a very useful means of palliation of malignant œsophageal stricture

I was very interested in the remarks of Mr Jamieson and his colleagues (April 23), who report two cases in which the upper "funnel" end of the tube eroded the wall of the œsophagus I have not myself encountered this complication, but have been aware of the possibility, and for some time have cut off a considerable portion of the rim of the funnel (which is coloured blue) in order to reduce its size Is the English œsophagus less capacious than the French, one wonders?

It is important to insert as large a tube as conveniently possible in order that it may be pulled down and jammed well into the growth This manœuvre is, I think, best controlled by following the passage of the tube through an œsophagoscope If the tube is pulled down too far the funnel will kink and itself cause an obstruction

In my experience the Mousseau-Barbin tube provides by far the best palliation for an inoperable cancer of the œsophagus Souttar's tubes are often dangerous to insert, and tend all too frequently to slip through the constricted area It may also usefully be inserted at thoracotomy when a growth proves to be unresectable

Finally, one has to remind oneself that palliation of a malignant stricture is not curative, and one should not expect too much from any one method Relief of the distress of extreme dysphagia should always be achieved whenever possible, but it seems to me that one must beware that one does not merely substitute for it a more prolonged agony Sometimes heavy sedation alone can be more merciful for these unfortunate patients The decision is often very difficult

Liverpool

B J BICKFORD

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[1] Jackson, D, Oakley W G *Lancet*, 1959, ii, 752
[2] Walker, J *ibid* 1958, ii, 641
[3] Graham, G *ibid* 1938, ii, 1

Parliament

Royal College of Physicians of London

ON May 9 at the second reading of this Bill Dr BARNETT STROSS moved its rejection,[1] though he sympathised with its objects He did so to obtain time for a debate on the constitution of the college It was not his intention to dictate to the college, but he asked it to think again about grievances felt by many of its members One of these was the procedure for the election of fellows

Fellows, he explained, were elected, or, as some people felt, selected, from the members, but they were elected only by the existing fellows and not by members Members could be put forward for fellowship only by other fellows and not by a member The list of those who were so sponsored did not reach the council of the college directly Two committees screened the names Members did not think it reasonable that when their names were put forward in the ordinary way by fellows for a fellowship their names should not go forward directly for ballot

The fellowship was an important and graceful distinction, but there was another implication, too, for members told him that in their view merit awards more easily followed fellowship Therefore, they felt nervous of criticising the constitution of the college or the method of election for fear that they would become unpopular The 4000 members had two representatives on the council of the college Neither they nor any of the members had complained about the method of election to the fellowship Dr Stross found it alarming that the officers of the college should have no knowledge that there was any feeling about the matter

What was even more archaic was that a fellow had no vote unless he was present in person in London at the headquarters of the college Dr Stross understood that a normal attendance at a meeting was about 90, thus 10% of the fellows elected officers or fellows and made decisions Fellows who were in the provinces were at a disadvantage, and the many fellows scattered all over the world virtually could not vote at all

In response to an interjection Dr Stross said that he had received 8 letters from members He had been asked by members to say that they should have some right of government and, therefore, should have a vote They also thought that even if they did not have a vote, the fellows, at least, should have a postal vote

Sir WAVELL WAKEFIELD said that among all the letters he had received about the Bill, none contained a single complaint or grievance, but he realised that that did not mean that such grievances did not exist He hoped that the words said in the House would be seriously considered by those responsible for the running of the college

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[1] See *Lancet*, April 23, 1960, p 912

Mr Kenneth Robinson accepted that the college was a most distinguished body which had a long history of service to medicine in this country Nevertheless, it could not conduct its affairs totally insulated from the world outside He was in favour of a postal ballot among fellows, and he could not see any reason why members should not join in electing the officers of the college and perhaps of the council He did not think that 2 councillors out of nearly 4000 members was a fully adequate representation It was odd that no complaint had ever reached the college It was plain that so much depended on the decision of the hierarchy of the college that members would be rash indeed to voice their criticisms too loudly Criticism that he had heard had not been confined to members Indeed, fellows had said that they thought that it was excellent that a debate should take place in the House and that the structure and constitution of the college should come under review

Sir Malcolm Stoddart-Scott pointed out that to become a fellow was to receive an award for academic distinction That could be done only by selection It could not possibly be done by election Dr Stross had expressed the dissident and dissatisfied views of 8 members of the college There would always be somebody who fell below the line and would be dissatisfied and wish to have some other method of choice of fellows

Dr J Dickson Mabon said that we must not pretend that because the college had a great record it was completely without any defect that could be altered to make matters more in tune with the times No member was said to have complained to the college, but 12 had spoken to him and 6 had written He now understood why these people did not wish to go into print It smacked very much of an oligarchy dispensing patronage, that one must not offend Something was seriously wrong when men of medicine should be unable because of fear of their own incomes, position, or future prospects to speak up and make radical constitutional changes within their own organisation The college had categorically and officially refused to consider any reform of its constitution and practice That sort of self-satisfied, smug attitude was a wrong way for a distinguished college to conduct itself

Miss Edith Pitt, parliamentary secretary to the Ministry of Health, said that the objects of the Bill were unexceptionable and were greatly desired by a most respected section of the medical profession The opposition to the Bill had been based on matters which were not connected with the Bill in any way—namely, what was alleged to be the undemocratic attitude of the college, and particularly the way in which the fellows were selected from the members and the rule that members of the college were not allowed to vote in the fellowship election Whether they were justified or not, they had nothing to do with the merits of the Bill and they should be pursued within the profession The Minister understood that there was machinery which would enable this to be done Dr Stross thought that the machinery was extremely limited Nevertheless, the Ministry were advised that there was a vehicle through which these protests could be raised in the council by the standing committee of members The issues which had been raised by some members had no bearing on the matters contained in the Bill, which everyone felt were admirable She hoped that its purpose would not fail because of a discussion quite outside its province

Dr Stross said that he hoped that the college would study what had been said, and withdrew the amendment

Professions Supplementary to Medicine Bill

At the report stage on May 4, Mr Derek Walker-Smith honoured the undertaking which he had given at the second reading and moved amendments excluding speech therapists from the Bill The speech therapists continued to object to their inclusion, and he was sure that inclusion should be regarded as a privilege and not as a penalty and that entry should be by way of conviction and not compulsion The amendment would affect the composition of the Council to be set up by the Bill To maintain numerical equality between the representative members and the medical members, the 8 medical members must be reduced to 7 He proposed to do this by reducing the number of members appointed by the Minister of Health from 4 to 3 and to provide that of these only 1, instead of 2, must be a doctor

Though the statutory powers of subpœna which were originally in the Bill had been omitted by decision of the House this did not mean that the disciplinary committees would have no powers of subpœna Such committees exercised a jurisdiction of a judicial nature and were generally recognised as constituting tribunals, and the Supreme Court had at all times lent its aid to inferior tribunals where they themselves lacked the means of enforcing the attendance of witnesses If, as a result of the report of Lord Simonds' Committee, amendments fell to be made to the Bill in another place, they would come back to the House in the ordinary way of procedure If the report called for legislation in a wider and more general field than these supplementary professions, then that general legislation would govern the proceedings of these committees, albeit under the terms of a general Act and not under the terms of this Bill It was obviously bound to be some time before the Council and boards were set up under this Bill, before the initial registers were prepared, and before the disciplinary committees were functioning Before that time the matter could be dealt with in whichever way was appropriate

QUESTION TIME

How Many Patients?

Mr L A Pavitt asked the Minister of Health what review was being undertaken in his department of the maximum number of patients permitted for a general practitioner in the National Health Service, with a view to the formulation of policy on this matter prior to the negotiations with the medical profession arising from the Pilkington report —Mr Derek Walker-Smith replied The general medical services are constantly under review in consultation with the medical profession so that any need for improvement or modification may be revealed and dealt with as opportunities occur

Mr Pavitt Does the Minister realise that it is impossible for a G P with a maximum list of 3500 patients to give a high standard of medical care? That means that he has an average of 17,500 consultations a year If he works 365 days and takes in Christmas day and holidays as well, this works out at more than 50 consultations a day Is it not time that some bold initiative was taken by the Minister to couple the awards that the Pilkington Commission recommended with some improvements in general practice?—Mr Walker-Smith It is always important to try to achieve whatever improvements in general practice we can, and it may be that this matter of maximum lists could arise in the context of discussion in regard to distribution I would remind the hon Gentleman that he is going on the basis of the maximum list, whereas the average list is only 2282

Mr Kenneth Robinson Will the Minister go a little further and say that he himself or his representatives will raise the subject of the desirability of reducing doctors' lists when he discusses with the profession the distribution of the central pool?—Mr Walker-Smith It is a little early to anticipate the trend of the discussions which we shall be having with the medical profession, but I will certainly bear in mind what the hon Member has said

Pilkington Recommendations

Dr Donald Johnson asked the Minister to what extent the acceptance by the Government of the recommendations of the report of the Royal Commission as they stand, provided the doctors and dentists accepted them on the same basis, embraced the proposal for a special fund of £500,000 for differential payments to general practitioners, and whether, in the light of the controversial nature of this proposal, he would make it a matter for separate negotiation from the main body of proposals —Mr Walker-Smith replied Full acceptance of the Royal Commission's recommendations necessarily includes acceptance of the award proposals for consultants, but not the creation of a special fund for differential payments to general practitioners which would depend, as recommended by the Royal Commission, whether a scheme was agreed for its application. The distribution of the central pool would as hitherto be a matter for agreement between the Government and the profession

Mr **Kenneth Robinson** Is the Minister aware that the misgivings which have been expressed by hon Members opposite and by the profession about the merit awards for general practitioners are shared by this side of the House? Can he say why he took the step of announcing his acceptance of these recommendations as a whole before canvassing the views of the House? Is he aware that many of us have views on the matter which he might find helpful in his discussions with the profession?—Mr **Walker-Smith** The Government's offer to accept the report as a whole if the professions would do the same seemed to us to be a proper and equitable way in which to approach the matter If the hon Gentleman has in mind any proposals in the report which he thinks ought not to be followed, no doubt he will say so Our approach is that neither side should pick or choose the bits which happen to suit it best.

Salaries of University Teachers

In a written answer Mr **Heathcoat-Amory** said that he was satisfied that a revision of the salaries of academic staff at the universities was now necessary if regard was to be had both to salary increases in comparable professions and to the need to retain and recruit staff of adequate calibre during the forthcoming period of great expansion in the universities He had considered the University Grants Committee's recommendation for non-medical and preclinical staff, and he proposed to ask Parliament to provide the additional funds required to enable the universities to bring into effect, as from Jan 1, 1960, the following revised rates and scales of salary for full-time academic staff

NON-MEDICAL POSTS

Professors

Basic salaries of £2600 a year, with provision for supplementation allowing for a range of salaries up to £3600 a year

Readers and senior lecturers

A range of salaries with varying maxima up to £2425 a year, or in special circumstances to £2525 a year

Lecturers

Scales rising generally from £1050 × £50–£1400 × £75–£1850 a year

Assistant lecturers

A scale rising from £800 × £50–£950 a year

PRECLINICAL POSTS

Professors

Salaries ranging from £2600 to £3600 a year

Readers

Salaries within the maxima indicated below for lecturers

Lecturers

Scales of salary rising from £1050 × £100 to maxima ranging from £1850 to £2525 a year

The total consequential increase in the recurrent grants of the universities was estimated to be about £$3^1/_2$ million a year initially The U G C. were considering the position of clinical staff in relation to the conclusions of the Royal Commission and would in due course submit recommendations for them

Government Doctors in Malta

Mr J D **Cronin** asked the Secretary of State for the Colonies if he would make a statement on the circumstances of the recent strike of doctors in the Government service of Malta.—Mr **Iain Macleod** replied The strike arose over the appointment of a new deputy senior medical officer, and the administrative channels for dealing with the affairs of the Medical Department within the Government Secretariat The Medical Officers' Union advised the Government on April 30 of its intention to strike as from midnight the following day, without previously giving any notice of the existence of a dispute. An emergency medical service is operating Mr **Cronin** Was not this strike precipitated by the circumstance that the Government appointed a deputy senior medical officer contrary to the recommendations of the Joint Advisory Board? Was not this an act which showed a considerable lack of administrative tact, having regard to the general political situation and to the discontent which has been present in the medical profession there for many years?—Mr **Macleod** With respect I think that is only half the story, because the Government were also advised by the Public Service Commission to appoint the man whom they did appoint, and, in spite of the advice of the medical board that the post should be advertised, the Government felt that was not a proper thing to do for an administrative post, and that ordinary promotion should carry on That is what the Government did.

Corneal Grafting

Lord **Stonham** asked H M 's Government whether they were aware of the urgent need for cadaver eyes for corneal grafting and of the long waiting-list of patients requiring this treatment, and if, in the hope of increasing the number of donors, they would, through the publication of an explanatory leaflet, seek to inform the public of this need —Lord **St Oswald** replied Inquiries made of hospital boards last year showed no general shortage, but some notable local difficulties In the view of the Government these needs are best met not so much by general publicity aimed at the future as by improving or extending the existing arrangements by which large neighbouring hospitals supply the corneal grafting centres Lord **Stonham** Is the noble Lord aware that at Moorfields, the largest centre for corneal grafting in the country, there is a waiting-list of never less than 100 cases, and that these people have to wait as long as eighteen months in unnecessary blindness?—Lord **St Oswald** I was aware of the figures at Moorfields The areas where supplies are not considered adequate are North London, Sheffield, Manchester, and Liverpool The position in those places has been kept under review and supplying hospitals reminded of the need.

The Earl of **Arran** May I, as a governor of Moorfields Hospital, confirm the situation Furthermore, may I ask whether the noble Lord is aware that this lack in donor material is entirely due to the restrictive operation of the Corneal Grafting Act 1952? Would he perhaps ask the Minister whether, in view of the sympathetic attitude of the public towards corneal grafting in general, he would consider giving unfettered effect to that Act? Lord **St Oswald** I think that what the noble Earl may be referring to is the power which is given to hospitals to rely simply on the absence of any known objection, but they have been advised by the Minister that wherever relatives are available their consent should be obtained I think it is generally felt that were the former method adopted it would cause great public perturbation and would not be popular, but would be considered as being arbitrary The Earl of **Arran** The present situation is even more embarrassing What happens now is that a patient dies and that, before his eyes can be used for this excellent purpose, his relations have to be asked—in other words, in the same breath they have to be told that their father, brother, or husband has died—can his eyes be used? Lord **Stonham** Would the noble Lord not suggest to the Minister that when people come into hospital and are asked to sign an agreement for postmortem the words should be added to the form that they are willing, in the event of their decease and providing their relatives have expressed no objection, for their eyes to be used for therapeutic purposes?—Lord **St Oswald** My Lords, I am entirely in sympathy with the noble Lord's aims in regard to this matter, as everybody must be. I will certainly put forward his proposal to the Minister

Superintendents of Mental Hospitals

Mr **Walker-Smith**, the Minister of Health, has decided to make regulations revoking the National Health Service (Superintendents of Mental Hospitals, &c.) Regulations, 1948, as from the date of the coming into force of the main provisions of the Mental Health Act, 1959 The effect will be to put psychiatric hospitals in the same position as other hospitals in that there will be complete discretion whether or not a superintendent should be appointed The new regulations will preserve the contractual rights of superintendents actually in post.

Obituary

SYDNEY WENTWORTH PATTERSON

M D Melb , D Sc. Lond , F R.C.P

Dr S W Patterson, lately senior physician at Ruthin Castle, died on May 1 at the age of 78

He was born in Melbourne and he was always proud to consider himself a " good Australian " He qualified in 1905, and hard work, partly in remote country practice, enabled him in 1912 to come to University College, London, and work under Prof E H Starling (whose daughter he later married) With Starling, he published work which is still regarded as important on cardiac output, heart-rate, and diabetes The outbreak of war interrupted his physiological research and he served in France with the Australian Voluntary Hospital Later he became assistant adviser in pathology to the B E F

In 1919 he went back to Melbourne as director of the Walter and Eliza Hall Research Institute, but in 1923 he returned to this country to join the staff of Ruthin Castle Clinic in North Wales as the colleague of Edmund Spriggs An old friend, Dr J H Anderson, shortly followed him from Adelaide Together the three men formed a successful team they all cared for patients, and Patterson made a special contribution to the scientific and technical side of the work He became senior physician in 1944 and retired only two years ago

Patterson often spoke at meetings of the Association of Physicians, the Gastroenterological Club, of which he was president in 1953, the Medical Society of London, and the Heberden Society He was Bradshaw lecturer at the Royal College of Physicians in 1941 He also published many papers and contributed articles to medical textbooks on widely differing subjects, but latterly most of his writings were on the alimentary system

E A S writes

" With a patient Patterson was kind, thorough, perceptive, and astute He talked discursively and had a curious mannerism by which the construction of a sentence would be changed in midflight, but his written reports were able summaries, and he vigorously pruned redundancies in his juniors' writings He had a scholar's mind It was, or seemed to be, a delight to him to discuss critically a physiological review with a student forty years his junior, or to search the British Museum and the Welsh National Library for old plans of Ruthin Castle and share with others his learning about local history Such things, after his family, were his real interests, and when a very late retirement came, he chose to spend his old age in the laboratories of University College, London, in active experimental research on wound-healing with Prof J Z Young

" Patterson's industry was phenomenal, embracing his clinical and scientific work and in later years a good many administrative and financial responsibilities All who knew him admired the energy he threw into the affairs of Ruthin Castle when some seven years ago its future, because of the impact of the health service, was temporarily uncertain Real relaxation—except when he was with children—he seemed to find difficult And his vigour off duty in the vegetable garden or the apiary or at the clock-repairing bench was hardly less remarkable than that at work "

Dr Patterson is survived by his widow, their four daughters, and a son who is a plastic surgeon at Oxford

CECIL HUGH MYDDLETON HUGHES

O B E , M B Lond , F F.A R C S

Dr Cecil Hughes, consulting anæsthetist to King's College Hospital, London, died at his home in Hove, Sussex, on May 2

He was educated at Westminster School and at the Westminster Hospital In 1900 he joined the South African Field Force and was posted to the Imperial Yeomanry field hospital He had the surprising experience of being captured by the famous Boer general, de Wet, in person and of making his escape After qualifying in 1903 Hughes held house-posts at Westminster before he was appointed administrator of anæsthetics, a post which he held until in 1914 he was appointed assistant anæsthetist to King's College Hospital He was also anæsthetist to the Seamen's Hospital, Greenwich, the Samaritan Free Hospital, the National Dental Hospital, and the Bethlem Royal Hospital In the 1914-18 war he was appointed consultant anæsthetist to the Royal Navy, with the temporary rank of surgeon-commander, and he served at the Royal Naval Hospital, Chatham, where he gave anæsthetics for Sir Watson Cheyne He was appointed O B E at the close of the war In 1921 he became senior anæsthetist and lecturer at King's, and when he retired from the staff in 1936 he was appointed consulting anæsthetist In the late war he returned to the King's sector and undertook anæsthetic duties at the Leatherhead Emergency Hospital

He was both president and secretary of the section of anæsthetics of the Royal Society of Medicine, and during his term as secretary he was responsible for the arrangements for the centenary of the death of Henry Hill Hickman, and it was largely due to his endeavours that the Hickman medal for outstanding service to anæsthesia was instituted

F F C writes

" As an anæsthetist, Hughes was an artist rather than a scientist He refused to administer deep ether anæsthesia and confined himself to chloroform-ether mixture and spinal analgesia. He was a master of the art of light anæsthesia and enjoyed teaching this almost forgotten technique to his students, using a drop bottle and a Schimmelbusch mask covered with a single layer of lint He insisted on attention to detail and woebetide the student who could not describe to him the signs of anæsthesia

" Hughes was gentle and polite to everyone, patients, students, and staff alike He was an ideal host who gave the impression that the comfort of his guests was his sole concern, and he was careful to make light and pleasant conversation to put entirely at his ease the junior whom he was entertaining His fatherly, kindly manner earned for him the nickname of ' Daddy ' "

IRENE YATES

M D Lond , M R C P , D P M

Dr Yates, formerly psychiatrist to the Queen Elizabeth Hospital for Children, Hackney, and the Elizabeth Garrett Anderson Hospital, died in London on April 23 after many years of increasing physical disability

She was born in 1894, the youngest of eight children of a Protestant family in Southern Ireland She was educated at Alexandra College in Dublin and at the London School of Medicine for Women After qualifying in 1918 she held house-appointments in London at her teaching hospital, the Brompton Hospital, and the National Heart Hospital She was appointed assistant physician to the Elizabeth Garrett Anderson Hospital, but within a few years a long illness compelled her to resign After her recovery she decided to take up psychological medicine and she worked at the Maudsley Hospital, taking the D P M in 1932, and at private mental homes at Lincoln and Bristol In the mid '30s she was reappointed to the staff of the Elizabeth Garrett Anderson Hospital, this time as psychiatrist She was also appointed psychiatrist to the Queen's Hospital for Children but her work was again interrupted by illness, and after the outbreak of war she decided that she would do more useful work among schoolchildren in Somerset than in partially evacuated London While in Somerset she began to have neurological symptoms, and though she struggled on till after the end of the war, her life from that time onwards was one of increasing physical disability

H M M M writes "As a student Irene Yates was popular, she was gifted socially and intellectually, with a quick Irish wit, and she was a hard worker—but before she graduated she had a period of diplopia, presumably the first symptom of the disseminated sclerosis from which she died over forty years later She maintained to the end her power to jest at her own troubles, her human interest in relatives and friends and those about her, as well as in the happenings in the world outside the four walls of her sickroom A verse she sent to a friend one Christmas may well stand as epitaph to a gallant doctor and patient

> Sow as you will, reap as you sow
> Labour is hard, rich harvests slow
> Storms may flood, and drought may burn,
> Good crops soon to ruin turn,
> But seed and waiting ground remain,
> Courage and will to start again
> Whether this year bring good or ill,
> May we never lose hope and keep
> Happiness still

Diary of the Week

MAY 15 TO 21

Monday, 16th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W 12
4 P.M Prof C H Stuart-Harris Virus Infections of the Respiratory Tract.

WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary s Hospital Medical School, W 2
5 P.M Prof R. R. Porter Structure of Gammaglobulin and Antibodies (Almroth Wright lecture)

Tuesday, 17th

ST MARY'S HOSPITAL MEDICAL SCHOOL
5 P.M Dr R R. Willcox Vaginitis Caused by Trichomonas and Candida Infestation.

SOUTH-WEST LONDON MEDICAL SOCIETY
8.30 P.M (Bolingbroke Hospital, S W 11) Sir Eric Riches Carcinoma of the Bladder (Bolingbroke lecture)

Wednesday, 18th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 15 P.M. *General Practice* Bishop of Durham The Relation Between Parish Priest and Family Doctor

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M Prof Robert Knox Strategy and Tactics of Chemotherapy

ROYAL FREE HOSPITAL, Gray's Inn Road W C 1
5 15 P.M. Dr Alfred Gellhorn (New York) Medical Aspects of Cancer

INSTITUTE OF DERMATOLOGY, Lisle Street, W C.2
5.30 P.M. Dr J O Oliver The Hæmopoietic System in Skin Diseases

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W.3
5 P.M Dr N S Plummer Bronchopulmonary Mycetomas

UNIVERSITY OF BIRMINGHAM MEDICAL SCHOOL, Birmingham, 15
5 P.M. Sir Dugald Baird Evolution of Modern Obstetrics (First of two Ingleby lectures)

Thursday, 19th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M Professor Stuart-Harris Virus Infections of the Respiratory Tract

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26, Portland Place, W 1
7.30 P.M. Dr G S Nelson Schistosomes as Zoonoses in Africa

LONDON JEWISH HOSPITAL MEDICAL SOCIETY
8 15 P.M. (11, Chandos Street, W 1) Dr J A Gorsky An Historical Inquest and Exhumation.

UNIVERSITY OF BIRMINGHAM MEDICAL SCHOOL
5 P.M. Sir Dugald Baird Evolution of Modern Obstetrics (Second of two Ingleby lectures)

HONYMAN GILLESPIE LECTURE
5 P.M (University New Buildings, Teviot Place, Edinburgh) Dr H W C. Griffiths Crush Injuries of the Chest

UNIVERSITY OF ST ANDREWS
5 P.M (Queen s College, Dundee) Prof Thomas McKeown Human Prenatal Growth

Friday, 20th

ROYAL SOCIETY OF MEDICINE
5.30 P M *Epidemiology and Preventive Medicine and Comparative Medicine* Dr C H Andrewes, Mr H V Thompson, Miss Miriam Rothschild Myxomatosis in Britain

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M Mr Ian Orr Selection of Operation for Peptic Ulcer

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, London, W C.1
5.30 P.M Prof F C Ormerod New Concepts of the Function of the Cochlear and Vestibule

INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W C 1
4.30 P.M Dr Denis Williams Syndromes of the Basilar Artery

Saturday, 21st

SOCIETY FOR THE STUDY OF INFECTIOUS DISEASES
11 A.M. (Ruchill Hospital, Glasgow) Opening of one-day meeting

Notes and News

EMPIRE RHEUMATISM COUNCIL

IN 1959 the Empire Rheumatism Council spent £56,000 on research, compared with £4600 in 1951 This progress is welcome, states Dr W S C Copeman, the chairman, in the report for 1959,[1] since every year 730,000 employed persons in Britain claim sickness benefit by reason of rheumatism, 27 million working days are lost, and the cost of the resulting absenteeism is estimated at £80 million The Council is certain that the causes of rheumatism can be established if research is continued and developed

Projects sponsored by this Council include the establishment of an electron-microscopy unit at St Thomas's Hospital Medical School, London, under Dr D V Davies, the professor of anatomy, the formation of an industrial rheumatism unit under Dr J J R Duthie, of Edinburgh, to study the social and economic effects of the disease in industry, and the setting up of a mobile field survey unit, the only one of its kind in the world, under Dr J S Lawrence Surveys by this unit have shown that one person in twenty in Britain has at one time or another suffered from an acute form of rheumatism (polyarthritis) This occurs most commonly towards the end of winter, although often severe enough to confine the patient to bed, it often disappears without permanent arthritis or heart-disease, and it is therefore important to distinguish this from the more serious forms

Degeneration of intervertebral discs, a common complaint among manual workers, is sometimes connected with rheumatoid disease These cases must be diagnosed so that correct treatment is given

Work to determine the mode of action of aspirin is being carried on by Mr R. J Ladd at University College, London, who is studying its effect on blood-flow, by Dr J A. Hicklin at London Hospital Medical College, working on potassium exchange, and by Dr V Moses, who has shown that it inhibits enzyme synthesis with a consequent effect on both carbohydrate and protein metabolism

Expanding activities are also reported from the Commonwealth In Canada they are carried on through the Canadian Arthritis and Rheumatism Society, in Australia through the Australian Rheumatism Council (both Canada and Australia have separate professional associations, similar to the Heberden Society in the United Kingdom), and in New Zealand through the New Zealand Rheumatism Association (a combined medical and lay body) It is hoped to form a Council in South Africa in the near future

AN EXPANDING INDUSTRY IN RADIOISOTOPES

THE talents of the versatile radioisotope are more and more in demand all over the world—in medicine, in biological and many other kinds of research, in industry To meet some of this demand it is the special function of the Radiochemical Centre, a part of the United Kingdom Atomic Energy Authority, to produce and distribute the many radioisotopes and related products made available by the Authority for civil purposes This commercial service radiates from Amersham, in the Chiltern Hills, 25 miles from London, and is available to all countries of the world Until March of last year the arrangements for producing and marketing radioisotopes were shared between the Radiochemical Centre and the isotope division of the Atomic Energy Research Establishment at Harwell At that time the scope of the Radiochemical Centre was extended to form a single comprehensive organisation with headquarters and principal laboratories at Amersham. During the first year under this new arrangement, the Centre handled some 35,000 consignments of radioisotopes, to a total value of over £1 million 60% of the products went abroad

Another stage in the expansion of the Radiochemical Centre was marked last week when two new laboratories were inaugurated by Sir Cyril Hinshelwood, P R S

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[1] Issued by the Council, Faraday House, 8, Charing Cross Road, London, W C.2

Royal College of Physicians of Edinburgh

At a meeting of the college on May 3, with Dr A Rae Gilchrist, the president, in the chair, the following were elected to the membership

E McC McGirr, R N Johnston, D S Smith, Battulapalli Ananta Ranga Rao, Robert Lamb, N E Loos, F D Honneyman, E A M Wood, T C Nicol, Anantanarayana Ramasubramanian, J K Davidson, Bashir Hasan Khan, Narayan Shamsunder Dixit, Jagadish Narayan Mishra, Majid Ali Jafri, Sheila Pereira, J S Madden, I W Pinkerton, Isabella C Ferguson, W G Wenley, Bryan Ashworth, Pamela M Lambden, Ralph Shulman, Poi Kwong Wong, R G Sourjah, G J Addis, Kalvyn Schoeman Van Eeden, Benjamin Cooper, P D Moylan, Kantibhai Chaturbhai Patel, P A Barker, Sharda Ranjan, Surinder Kumar Vohra, John Johnson, Gopal Chand Pandey, J H P Willis, Om Parkash Thaman, I H Jones, J N G Davidson, B S L Kidd, B R Knowles, Gopalakrishna Thagathuveettil Damodara Panicker Pillai, Braja Mohan Goswami, Peter McDonald, Alexander Pringle, Enid J Cartwright, Aung-Than-Batu, Gilbert Obiafo Onuaguluchi, Aswathnarain Nagaraj, Sudarshan Kumar, Brajjeshwar Mittra, A E Charaoui

Royal College of Surgeons of Edinburgh

At a meeting on May 6, with Prof John Bruce, the president, in the chair, the following were admitted to the fellowship

J G Allman, J H F Batstone, Niren Bhaduri, W H Bisset, D G Calvert, Kenneth Chambler, R G Clark, Michael Cohen, B C Cohney, D H Coop, Delia M H H Cothay, Chhaganlal Nanji Dedhia, E E Denman, H C De Wet, Mohamed Magid Ismail Fakhr, A D George, Mavis G Gilmour, Peter Gortvai, Prithi Singh Grewal, J M S Hague, M A Henderson, W H Huffam, K F Hume, E G Ibach, J D Iswariah, T E Jeffreys, C O R. King, W J Laister, G J Little, Peter Mactaggart, D J McWilliams, Hashim Makki, G B Markey, B C Meehan, Bharat Vrajlal Mehta, J M Mistry, Rajendra Nath Mullick, G A I Namsoo, Cheuk Hing Ng, J A O Reilly, W McN Orr, P Mathai Paulose, Vithal Gangadhar Phansalkar, W J Poate, L W Poole, Abdul Aziz Qazi, R A Rivett, J S Scougall, D K Sutton, Chee Yong Tan, D S Thomson, Jayaweera Bandara Wedande, S B Williams, Kean Hong Yeoh

Royal Faculty of Physicians and Surgeons of Glasgow

At a meeting on May 2, with Mr Arthur Jacobs, the president, in the chair, the following were admitted to the fellowship, *qua* surgeon

A K Bain, D Pui-Chee Chan, W G Millar

Postgraduate Medical School of London

South Africa has raised £50,000 towards the building appeal of the school The money has been given by business concerns and private individuals in response to an appeal launched in Johannesburg a year ago

Nuffield Foundation

The Foundation has allocated £60,000 to form a " unit for the history of scientific ideas " which will produce educational films and books under the direction of Dr Stephen Toulmin, formerly professor of philosophy at the University of Leeds The first aim of the unit will be to produce a basic collection of teaching films and textbooks for use in sixth forms and introductory university courses in the history and philosophy of science

Beit Fellowships

The following elections to fellowships have been made

Junior fellowships (£900 a year) —D C Watts, M SC Lond (at the department of biochemistry, University College, London), J R Casley-Smith, M B , B SC Adelaide (at the Sir William Dunn School of Pathology, Oxford) , P F Fottrell, M SC N U I (at the tissue culture laboratory, biochemistry department, University of Glasgow), A J Rowe, M A Cantab (at the Department of Colloid Science, Cambridge), C F V Seaman, PH D Cantab (at the Department of Medicine, Cambridge)

Senior fellowship (£1300 a year)—J R Tata, M SC Bombay, D SC Paris (at the National Institute for Medical Research, Mill Hill, London)

World Health Assembly

Opening the thirteenth World Health Assembly in Geneva on May 3, Sir John Charles, chief medical officer to the Ministry of Health, the outgoing president, said that today W H O was concerned with two main groups of problems first, environmental, nutritional, and epidemiological questions in the emergent States, and secondly the needs of the middle-aged and elderly in the other communities It was a mistake to think that these were entirely separate sets of problems, they required the same approach for their solution—research, education, and cooperation

Dr H B Turbott, director-general of health, New Zealand, was elected president of the Assembly

British Institute of Radiology

On Thursday, May 19, at 8 P M , at the institute, 32, Welbeck Street, London, W 1, Dr V E Cosslett will give the Silvanus Thompson lecture He will speak on X-ray microscopy

Mental After Care Association

The annual general meeting of this association will be held on Tuesday, May 17, at 3 P M , at the Hall of the Worshipful Company of Haberdashers, Staining Lane, London, E C 2 The speakers will be Monsieur L C Picalausa, director-general of the Belgian Red Cross, and Dr Henry Yellowlees

Société Médicale Internationale de Photo-cinématographie et Télévision Endoscopiques et de Radio-cinématographie

This society will hold its annual congress on May 25 at 2 15 P M , at 1, Wimpole Street, London, W 1 The speakers will include Dr E Chérigié, Dr N Jaupitre, Dr M Noix, Dr Dubois de Montreynaud, Prof P Porcher (France), Prof van d Plaats (Holland), Prof R Janker (Germany), Prof Chevalier Jackson (U S A), Dr J J Stevenson, and Mr H G Hanley

Zoological Society of London

The Ford Foundation has made this Society a grant of 550,000 dollars (about £196,000) to endow research fellowships in animal reproduction The first awards will be made during the coming summer by a committee of experts and it is hoped that the Zoological Society fellows will have a secondary attachment to a university laboratory engaged in related work. Laboratories will be provided at Regent's Park by the society, and a Breeding Research Committee including Prof E C Amoroso, Prof F W Rogers-Brambell, Prof A St G Huggett, and Dr A S Parkes will supervise the work.

Surgeon Rear-Admiral W V Beach has been appointed an honorary surgeon to the Queen in succession to Surgeon Vice-Admiral Sir Cyril May

Dr D J West, senior registrar to the forensic unit, Maudsley Hospital, London, has been appointed assistant director of research at the Institute of Criminology, Cambridge

Brigadier H L Glyn Hughes will speak at the annual general meeting of the Elderly Invalids' Fund at Skinners Hall, 8½, Dowgate Hill, London, E C 4, on Thursday, May 19, at 5 30 P M

The annual dinner of the Indian Medical Service Dinner Club will be held at the East India and Sports Club, St James's Square, London, S W 1, on Friday, June 10, at 7 30 p m Tickets may be had from the secretary of the club, Medical Room, Commonwealth Relations Office, Matthew Parker Street, S W 1

Appointments

DUCKSBURY, CHRISTINA F J , M.B Edin. assistant M O H. and school M O , Sheffield

MERCER, J C G , M B Edin., D C H medical superintendent, East Fife hospitals board of management

STEVENS, P R., M.R C S , D O consultant ophthalmologist, Blackburn and district group of hospitals

TOWNSEND, MARY, M B Lond , M.R C P , D C.H assistant M O H and assistant school M O , Dorset.

VALE, R. J , M B Lond., M.R.C.P , F F A R.C S , D.A consultant anæsthetist, Chelsea Hospital for Women, London

WALLIS, ETHEL M , M B Edin., D OBST , D P H. senior assistant M O H., Oxford

WHEBLE, V H , B M Oxon, F.R C S E consultant traumatic and orthopædic surgeon, Ashton, Hyde, and Glossop group of hospitals

The Hospital for Sick Children, Great Ormond Street, London

MISHRA, J N , M.B Patna, M.R C.P.E , D C H medical registrar

PISARELLO, J C , M D resident officer, departments of neurology and neurosurgery

RANSOME-KUTI, OLIKOYE, M B Dubl assistant M O , Tadworth Court

Liverpool Regional Hospital Board

BUXTON, P H , M D Cantab , M.R C.P consultant pathologist, regional neurosurgical unit, Walton Hospital

CLARKE, E E , M D N U I , M R C.P , D P.M assistant psychiatrist, Rainhill Hospital

COULSHED, NORMAN, M D Lpool, M.R.C.P consultant physician in cardiology, regional cardiac centre, Sefton General Hospital

SCANLAN, E P , M B N U I , D OBST , D P.M assistant psychiatrist, Rain hill Hospital

SLATTER, K H , M.D Lpool, M R.C P consultant neurologist, regional neurosurgical unit, Walton Hospital

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THE NATURE OF ESSENTIAL HYPERTENSION

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OF THE MEDICAL RESEARCH COUNCIL'S PNEUMOCONIOSIS RESEARCH UNIT, LLANDOUGH HOSPITAL, CARDIFF

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OF THE M R C. CLINICAL GENETICS RESEARCH UNIT, INSTITUTE OF CHILD HEALTH, GREAT ORMOND STREET, LONDON, W C.1

G S C Sowry
M D Lond , M R C P
PHYSICIAN, EDGWARE HOSPITAL, MIDDLESEX

Recent correspondence in this journal has shown that opinion is divided between two views of the nature of essential hypertension

The older view, to which it seems that most subscribe, is that essential hypertension is a specific disease entity, and that subjects with and without the disease can be separated sharply on the basis of their arterial pressures This hypothesis conforms to the general belief that disease represents a qualitative deviation from the norm, and it has led to investigations on inheritance assuming that the disease is the manifestation of a single gene believed to behave as a mendelian dominant

The new view, for which we and our colleagues are largely responsible, is that essential hypertension represents a quantitative and not a qualitative deviation from the norm, that there is no natural dividing line between normal and abnormal pressures, and that any attempt to divide pressures sharply into normal and abnormal is artificial Should it prove that the genetic element in hypertension—indeed in the determination of arterial pressure generally—is multifactorial, this hypothesis would receive strong support Blood-pressure would then be inherited as a graded character like height, and the mode and degree of inheritance would be the same whether the pressure is below the norm or so far above it as to constitute essential hypertension This hypothesis is in full accord with the quantitative relationship between arterial pressure and its adverse effects on expectation of life and on the cardiovascular system (see Pickering 1955)

Controversy centres around the nature of the inheritance It was reopened by Platt's (1959a) article in which he showed clearly that the frequency distribution curves for sibs, aged 45–59, of propositi, aged 45–59, with essential hypertension, had dips at 150 systolic and 90 diastolic "which is exactly the figure most commonly chosen by clinicians as the dividing line between normal and high blood pressure in middle aged subjects" Platt took his data from the work of Sobye (1948) and of Hamilton et al (1954c) He concluded

> "The final proof as to whether essential hypertension exists as an entity will have to wait until a prospective survey lasting at least twenty years has been made over a large unselected population to see whether with advancing years they segregate into two groups, those whose pressures steeply rise and those whose pressures remain little affected Until this is done I shall remain unconvinced that the work of Pickering and his colleagues has disposed of the concept of the entity of essential hypertension"

Platt's paper was followed by one of Morrison and Morris (1959) which favoured the view that hypertension without apparent cause is inherited as a dominant and is a specific disease *The Lancet* (1959) commented "We find this new evidence that essential hypertension is a specific disease both convincing and more in keeping with its clinical behaviour"

Here we re-examine the two hypotheses and the controversial genetic evidence

The Evidence Re-examined

We begin by considering the evidence for the hypothesis that essential hypertension is the expression of a single gene behaving as a mendelian dominant This hypothesis has been stated by Platt as follows

> "This concept of essential hypertension as an inherited tendency to develop high blood-pressure in middle life presumes that there are two populations, one in which blood-pressure rises significantly in middle age, often reaching heights at which it seriously contributes to mortality, and another population in which blood-pressure rises only very little if at all with increasing years"

The evidence put forward for this hypothesis is the occurrence of the disease in three generations, equality of numbers of affected and unaffected sibs, and bimodality of frequency-distribution curves in sibs, we may also consider the rate of rise of pressure with age and the problem of gene frequency

THE DISEASE IN THREE GENERATIONS

Weitz (1923) and Platt (1947) have both been impressed by this evidence for mendelian dominant behaviour The evidence is either the occurrence of hypertension, or death from stroke or sudden heart-failure, in three successive generations If we accept, as they do, a pressure of 160 or over as proof of hypertension, then we may calculate the probability of such an occurrence in an unselected group of families without making any assumptions about inheritance The frequency of pressures of 160 and over in Hamilton's (1954a) population sample aged 55–59 was 23% in men and 38% in women Assuming both parents and all four grandparents of a given individual achieve this age, the chances of the pressure exceeding this value in one of his parents and one of his corresponding grandparents, is then 37% We attach no importance to this precise figure, since it depends critically on the arbitrary figures chosen to represent hypertension, on the circumstances in which blood-pressure was measured, and on the age-group considered However, it is evidently possible, by making up families at random, to obtain a greater frequency of hypertension in the two generations preceding the propositus than indeed was reported as evidence for inheritance by Weitz and Platt For Weitz (1923) observed 6 families out of 82 considered, and Platt (1947) 4 out of 54—a proportion that is scarcely strong evidence for dominant inheritance

RATIO OF AFFECTED AND UNAFFECTED OLDER SIBS

This was studied by Weitz (1923), who found 1 1 ratio between them when 160 systolic was taken as the dividing line, and sibs who had died from heart-disease and stroke were added The ratio is clearly determined by the choice of a dividing line and the age-group to which it is applied In Hamilton et al 's (1954a) population sample, a 1 1 ratio can be got by choosing a similar dividing line and choosing women in the seventh decade

ARE THE DISTRIBUTION CURVES OF BLOOD-PRESSURES IN FIRST-DEGREE RELATIVES BIMODAL ?

Platt (1959a) plotted the frequency distribution of sibs aged 45–59 years of propositi aged 45–59 years with hypertension Those derived from Sobye's (1948) data had a conspicuous dip at 140 and 150 systolic and at 90 diastolic those derived from Hamilton et al 's (1954c) data had dips at 150 systolic and 90 diastolic We have found that these dips are not due to combination of the sexes, since they persist in the same places when the sexes are separated, even though the distribution curve for females is, as a whole, shifted to the right Besides bimodality, chance or digit preference might be responsible for these dips Apart from two superimposed separate populations, there are other causes for bimodality We have therefore examined the frequency-distribution curves for each sex and in all decades in both Sobye's and our hypertensive relatives and in our control relatives with these possibilities in mind

Relatives of Hypertensive Propositi

The first-degree relatives of all Hamilton's and Sobye's hypertensive propositi have been divided into males and females, and frequency distribution curves have been plotted for age-groups 10 to 29, 30 to 39, and each succeeding decade to the eighth For systolic pressures a dip at 150 was found in 9 out of 12 curves in Sobye's series and in 3 out of the 12 curves for Hamilton's series For diastolic pressures the corresponding frequencies of a dip at 90 are 8 out of 10 times in Sobye's series, 2 out of 10 times in Hamilton's series, the distribution curves for diastolic pressure in age group 10–29 were so narrow, and Sobye's series had so few points, that they have been omitted As an approximate index of the size of the dip, the number of subjects having pressures of 150+155 mm Hg was expressed as a fraction of the mean for the numbers respectively at 140+145 and 150+155 The same has been done for numbers with diastolics of 90+95 as fractions of those 80+85 and of 100+105 respectively The results are for Sobye's series

Systolic
All relatives, 0 49
Relatives aged 45 to 59, 0 45
Diastolic
All relatives, 0 55
Relatives aged 45 to 59, 0 61

and for Hamilton's series

Systolic
All relatives, 1 02
Relatives aged 45 to 59, 0 90
Diastolic
All relatives, 0 94
Relatives aged 45 to 59, 0 73

Thus the dips are much more conspicuous in Sobye's series

Fig 1 compares the frequency-distribution curves of diastolic pressure in females in the successive age-groups of the two series The curves not only show the more constant dip in Sobye's series, they also show how constant in position it remains The same is true for the systolic curves As decade succeeds decade, the distribution curves move to the right and spread out—but the dips at 150 and at 90 tend to stay If these depressions represent bimodality, it is a very curious one, for the bulk of subjects seem to transfer themselves from one side of the dip to the other as age advances This bimodality cannot represent two populations in one of which blood-pressure rises little with age and in the other steeply In fact, if the dip is real it can mean only one thing—that the transition from pressures of 140 and below to those of 160 and above is achieved much more quickly at all ages than other transition of comparable size

Tables I and II from Miall's follow-up in the Rhondda Fach show the frequency distributions of change of systolic pressure over four years in females and males arranged according to the mean of the pressures recorded in the first and second survey Each distribution is remarkably regular and shows no sign of being separated into two parts, in females the mean change at 150 mm Hg is indeed slightly larger than in the adjacent groups, but to a small degree In males, 150 marks the beginning of an increase that continues steadily to 190 mm Hg

However, the real importance of these tables is their relevance to the single-gene hypothesis On this hypothesis even in four years there should be a clear segregation into those whose " pressures rise significantly " and those " whose pressures rise only very little if at all " No such segregation is seen

The constancy of these dips at 150 and 90 and their presence in both sexes makes it unlikely that they are due to chance

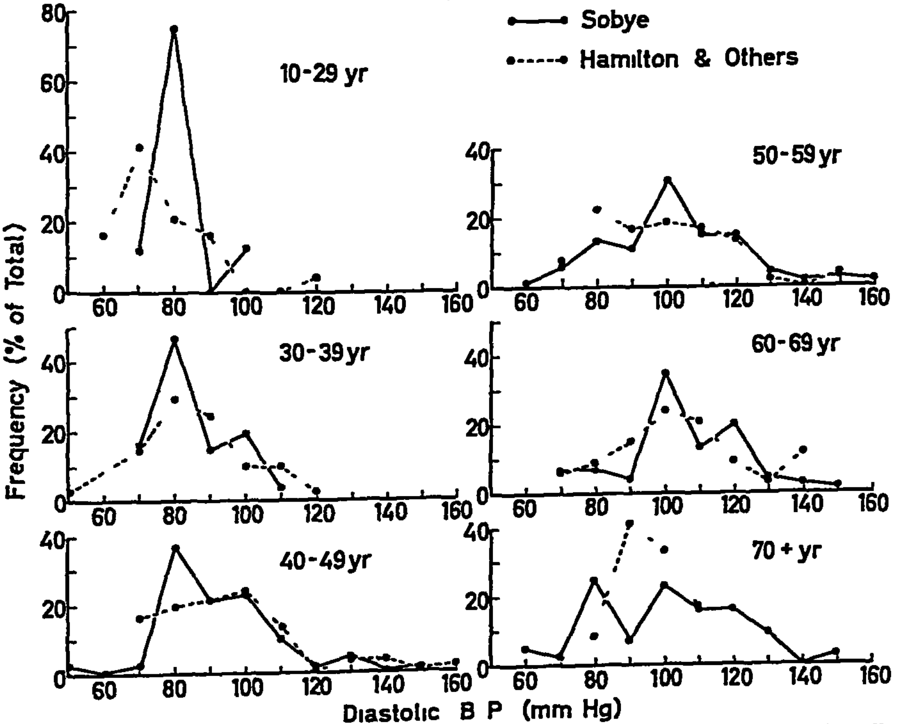

Fig 1—Female relatives of hypertensive propositi Frequency-distribution curves of diastolic pressure in successive age-groups
(Data from Sobye 1948 and Hamilton et al 1954c)

TABLE I—DISTRIBUTION OF CHANGES OF PRESSURE IN FOUR YEARS BY AVERAGE OF PRESSURES AT BEGINNING AND END OF PERIOD FEMALES, SYSTOLIC

Change of pressure in 4 years (mm Hg)	Mean of starting and final pressures (mm Hg)																	Total
	80–	90–	100–	110–	120–	130–	140–	150–	160–	170–	180–	190–	200–	210–	220–	230–	240–	250–	
70–80												1							1
60–											2	1	1	1					5
50–											2								2
40–						1	2	1	1	1			1	1	1	1	1	1	12
30–			2	9	4	6	3	3	1	2	4	1	1						36
20–		5	5	16	11	14	4	6	5	5	5	1		1					78
10–		4	16	34	26	18	10	6	3	3	2	2	2	1					127
0–		3	23	41	37	21	13	8	8	1	2	1					1		159
−10–		3	12	26	29	18	8	4	2	2		2			1				107
−20–			3	8	8	6	4	1	2	1			1			1			35
−30–		1		3	4	3	2			2		1							16
−40–		1					1	1	1	1					1		1		7
−50–														1					1
−60–																			
−70–																			
−80–													1						1
Total		17	61	137	119	87	47	30	23	18	17	10	7	5	3	2	3	1	587
Mean change		4 85	4 80	5 57	2 75	5 83	4 41	9 50	6 85	7 50	29 56	17 50	9 64	18 5	−0 83	12 50	2 50	42 50	

Conscious or unconscious discrimination against particular figures is clearly a possible explanation The frequency of such a practice is exemplified by the following instructions from an insurance company to their examining doctors " If the Systolic Pressure is 140 mm Hg or more, or the Diastolic Pressure is 90 mm Hg or more, please take further readings " This is not an unimportant consideration, since about a third of Sobye's and half of Hamilton's measurements were made by either family or hospital doctors

Both Sobye and Hamilton et al began their observations with the assumption that subjects could be divided into those with and without hypertension They thus had predominantly in mind the question " has the relative got hypertension or not? " and thus the unconscious incentive to assign borderline cases to one side of the line or the other Sobye worked out all his results in terms of this hypothesis, moreover, since Sobye made repeated measurements he had a greater opportunity to discriminate against borderline values than Hamilton and his colleagues, who took only one measurement Sobye states that " the values were not recorded at greater intervals than 5 mm Hg " " Measurements were undertaken at intervals of 5 minutes until basal and stable values were obtained which generally took ab 5 to ab 45 minutes The cuff was left on the arm but relaxed between measurements and the soothing and diverting conversation was continued " Despite the numerous readings taken, and his opportunity for fine measurement, 73% of the values he finally adopted of systolic and 74% of those for diastolic pressure end in 0 His, then, was rather a coarse assessment of arterial pressure, and the opportunity for digit preference to affect the numbers assigned to neighbouring 10s correspondingly great

Hamilton and his colleagues took their pressures to the nearest 5 mm Hg and took one reading They did not try to measure more closely than 5 mm because they doubted the significance of more accurate readings in view of the diurnal variability When, however, a single reading is taken, pressure in the cuff is raised to 200 mm Hg or over and allowed to fall until sounds first appear and then suddenly diminish—incidents which the observer correlates with the position of the mercury meniscus relative to the adjacent scale Here again there is scope for digit preference between adjacent 10 mm

The difference between the sizes of the dips at 150 and 90, and the greater opportunity for digit preference in Sobye's series, are evidence for this explanation

Relatives of Propositi Without Hypertension

Hamilton et al (1954c) collected this series as a control for the relatives of hypertensive propositi We have plotted the frequency-distribution curves for the same age-groups as for the hypertensive series but with the sexes combined Dips at 150 and 90 were not seen We have not tried to express the numbers at 150 and 90 as fractions of the means of adjacent groups above and below, because in this series the frequencies are falling at these points and the fractions would be misleading

The absence of any appreciable dip in the control series is against digit preference being the explanation of the dip in the hypertensive series However, this argument is not conclusive, because the curves for hypertensive relatives were much flatter at this point and dips were thus more easily displayed, and because in fact the dips were present only in 5 out of 22 of the corresponding frequency-distribution curves of systolic and diastolic pressure by decades in the hypertensive relatives

Our conclusion from a critical examination of this evidence is that the dips to which Platt has rightly drawn attention might represent bimodality, but they might also be due to discrimination against certain figures, or digit preference If they do represent bimodality it is not between two populations having the characteristic rates of rise of pressure with age postulated by Platt Because

TABLE II—DISTRIBUTION OF CHANGES OF PRESSURE IN FOUR YEARS BY AVERAGE OF PRESSURES AT BEGINNING AND END OF PERIOD MALES, SYSTOLIC

Change of pressure in 4 years (mm Hg)	Mean of starting and final pressures (mm Hg)																Total
	80–	90–	100–	110–	120–	130–	140–	150–	160–	170–	180–	190–	200–	210–	220–	230–	240–	
70–										1								1
60–											1							1
50–							1		2		1	1					1	6
40–			2	1	4		1			1	2	2			1			14
30–				3	3	8	4	4	4	1	1							28
20–		2	8	10	16	16	9	6	1	2	1							71
10–	1	2	17	32	31	24	11	3	3			2						126
0–		4	7	25	44	20	15	7	1	2	3							128
−10–			12	11	28	21	15	4	3	2			1					97
−20–			3	4	13	8	7		2	1								38
-30–				1	1	1			1									4
40–					1			1								1		3
50–																		
Total	1	8	49	87	141	98	63	25	17	10	9	5	1		1	1	1	517
Mean change	12 5	9 75	7 19	7 54	4 11	6 58	5 83	10 10	12 50	16 50	29 16	32 50	−7 50		42 50	−37 50	52 50	

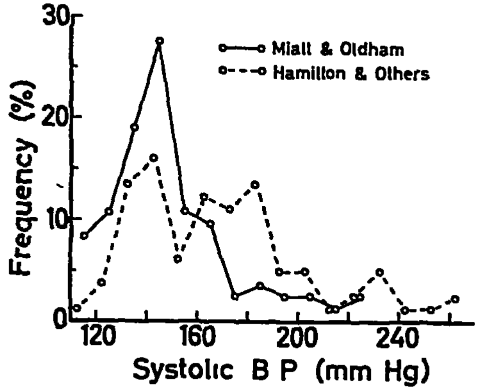

Fig 2

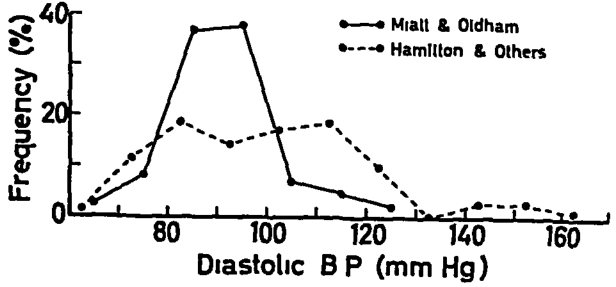

Fig 3

Figs 2 and 3—Frequency distribution for relatives aged 45–59 of propositi with hypertension aged 45–59

(Data from Hamilton et al (1954a) and from Miall and Oldham's survey in the Rhondda Fach and Vale of Glamorgan (1955, 1958)

both Sobye and Hamilton's group only tried to estimate arterial pressure to the nearest 5 mm Hg it seems unsafe to base any conclusions on arguments based solely or chiefly on distributions between adjacent 10 mm groups

The Evidence from Miall and Oldham's series

Miall and Oldham (1955, 1958) set out to explore the possibilities raised by Hamilton and his colleagues with two major improvements in technique their propositi were truly a random sample and a single observer (Miall) measured the arterial pressures to the nearest 5 mm Hg below

Figs 2 and 3 show the frequency-distribution curves for 84 sibs aged 45–59 derived from propositi aged 45–59 with diastolic pressures of 100 mm Hg or above, and the corresponding curves for Hamilton's series Miall and Oldham's readings show no preference for 0s, since, of the 83 systolic readings of 220 or below, 42 ended in 0, while of the 82 below 120 diastolic, 45 ended in 0 The curve for systolic pressure shows a slight flattening at 150, but does not seem bimodal, that for diastolic pressure shows no evidence of bimodality

Both systolic and diastolic curves for Hamilton's data show the dip to which Platt drew attention Quite apart from this they differ conspicuously from those of Miall and Oldham's data in being much flatter, owing to a less pronounced peak, and a considerable excess of values over 160 mm Hg systolic and 100 diastolic These differences clearly reflect differences in the frequency distributions of pressures of the two sets of propositi shown in figs 4 and 5 Miall and Oldham's propositi represent a " cut off " from a population sample, and, as might be expected, the frequency is maximal with the lowest pressures and sharply declines Hamilton's propositi, however, were drawn from patients presenting with symptoms They naturally show a pronounced deficiency at the lower and an excess at the higher pressures

The qualitative hypothesis provides no explanation for the differences between Miall and Oldham's first-degree relatives of hypertensive propositi on the one hand and Hamilton's on the other If propositi aged 45–59 with diastolic pressures of 100 and more have essential hypertension, as those who support the single-gene hypothesis aver, then the frequency-distribution curves for the Miall and Oldham and Hamilton relatives should be alike, allowing of course for irregularities due to small numbers That they are not is inexplicable on the qualitative hypothesis but is readily explained by the quantitative hypothesis The difference between the distribution curves for pressures of relatives in fact merely reflects the differences in the distribution of pressures of the propositi and seems to illustrate once again that it is not hypertension that is inherited but the degree of hypertension

We would conclude therefore that a comparison of Miall and Oldham's and Hamilton's data reveals features that are inexplicable by the qualitative but are in full accord with the quantitative hypothesis

RATE OF RISE OF PRESSURE WITH AGE

It is an essential part of Platt's hypothesis that what is inherited as an expression of the dominant gene is a tendency for the arterial pressure to rise faster with age than it does in those lacking the gene Hamilton and his colleagues found that the rates of rise of systolic and diastolic pressure with age did not differ significantly in (1) their population sample, (2) the first-degree relatives of propositi without hypertension, and (3) the first-degree relatives of propositi with essential hypertension, except for a faster rise of systolic pressure with age in the male hypertensive relatives

Table III summarises the rates of rise of pressure with age in relatives of propositi aged 45–59 with and without hypertension The sexes are combined since there was no material difference between them It will be seen that if relatives of all ages are considered, the rate of rise differs significantly between the two sets of relatives in Hamilton's series but not in that of Miall and Oldham When relatives aged 35 and over are considered separately, a similar trend is found, the difference being significant for systolic and nearly significant for diastolic in

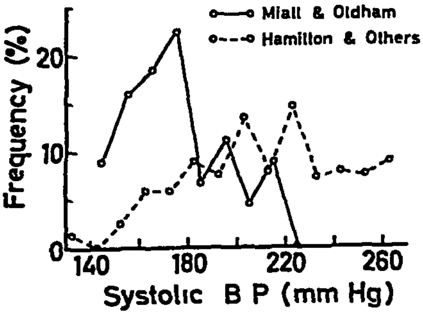

Fig 4

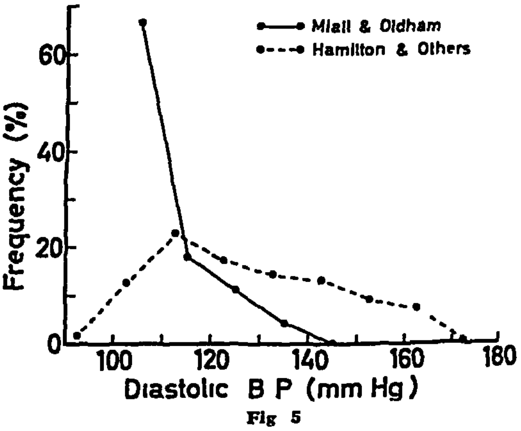

Fig 5

Figs 4 and 5—Frequency distribution of the blood-pressures in the propositi from whom the relatives shown in figs 2 and 3 were derived.

Hamilton's series but less pronounced in Miall and Oldham's series.

Two points require comment. First, in Hamilton's series the disparity between relatives of normal and hypertensive propositi is increased to the point of revealing a significant difference by restricting propositi to age-group 45–59. Second, a difference between the two sets of relatives is revealed in Hamilton's series but not in that of Miall and Oldham.

Now this is exactly what would have been expected on the quantitative hypothesis and on the known behaviour of blood-pressure with age. A given deviation from the norm at age 30 is represented by a much larger one at age 60. Thus if relatives resemble propositi, the higher the pressures of the propositi the steeper should be the slopes of the rates of rise of pressure with age in their first-degree relatives. The difference in the way propositi were chosen would account for the difference in rates of rise with age being greater in Hamilton's than in Miall and Oldham's series. Restricting the age-group of propositi would account for the differences between the present and previously published comparisons of Hamilton's series. Thus Hamilton and his colleagues were disturbed by the absence of any significant difference in the rates of rise of pressure with age in three of the four comparisons between normal and hypertensive relatives. They wrote (1954c):

TABLE III—RATE OF RISE OF BLOOD-PRESSURE (MM. HG) PER YEAR OF AGE IN FIRST-DEGREE RELATIVES OF PROPOSITI AGED 45–59

—	Propositi without hypertension	Propositi with hypertension	Difference
Relatives of all ages			
Systolic			
Hamilton et al.	0·855±0·129	1·276±0·149	0·421±0·213
Miall and Oldham	0·997±0·057	0·968±0·160	−0·029±0·150
Diastolic			
Hamilton et al.	0·408±0·080	0·549±0·090	0·141±0·129
Miall and Oldham	0·400±0·032	0·261±0·087	−0·139±0·090
Relatives aged 35 and over			
Systolic			
Hamilton et al.	0·780±0·189	1·512±0·242	0·732±0·325
Miall and Oldham	1·449±0·170	1·766±0·446	0·317±0·446
Diastolic			
Hamilton et al.	0·222±0·114	0·413±0·144	0·191±0·194
Miall and Oldham	0·219±0·087	0·212±0·248	−0·007±0·235

> "Figs. 3 and 4 appeared to show that the pressures of the youngest relatives of hypertensive subjects are divided from the norm to the same extent as their older relatives. The majority of the relatives are sibs and so resemble the propositi in age distribution; this means that on the average the younger relatives are derived from the younger propositi and therefore depart more greatly from the norm. Hence curves which should have shown increasing divergence have become artificially parallel."

While the new comparison may seem to fit Platt's hypothesis, it is thus also compatible with the quantitative hypothesis, from which indeed it could, as the quotation shows, have been predicted.

Now Platt's hypothesis implies that the rate of rise of pressure with age is entirely, or almost entirely, due to the presence, in the populations considered, of people carrying the hypertensive gene. There should thus be a considerable difference between the behaviour of the population at large, in which the rate of rise of those carrying the gene will be diluted by the much larger number of those without it, and the behaviour of the first-degree relatives of affected subjects who share a gene in 50% of cases.

TABLE IV—DISTRIBUTION OF THE MEAN DIASTOLIC PRESSURES OF 119 RELATIVES OF HYPERTENSIVES AND 59 RELATIVES OF NORMOTENSIVES (CRUZ-COKE 1959)

Age (years)	Relatives of normotensives		Relatives of hypertensives	
	No. of cases	Diastolic B.P. (mean and standard error)	No. of cases	Diastolic B.P. (mean and standard error)
10–19	5	65·0±1·75	22	75·1±1·45
20–29	18	71·0±1·65	38	78·9±1·44
30–39	13	75·1±2·40	19	88·8±1·64
40–49	7	76·4±2·09	17	89·0±1·66
50–59	11	81·3±2·65	15	95·3±2·14
60–69	5	80·0±5·10	8	93·6±2·89
	59		119	

The absence of such a difference between the relatives of Miall and Oldham's propositi whose pressures fall below and above the postulated division, and thus between those without and with the postulated specific gene, seems to be conclusive evidence against the qualitative hypothesis, at least in its present form.

Platt (1959b) has cited two papers showing that arterial pressure does not rise with age in certain groups.

Thomson (1950) studied the records of 3343 employees of the Metropolitan Life Insurance Company, whose arterial pressures had been recorded annually from age 40 to retirement at 60 in women and 65 in men. He divided them into three groups according to whether their arterial pressures at any time exceeded 140 systolic and 90 diastolic. Those who never exceeded these values were "normal", those who frequently exceeded them were "frequently elevated", and those who always exceeded them were "constantly elevated", they constituted respectively 74·2%, 14·4%, and 11·4% of the whole. That individuals behave differently in response to age is not disputed and was indeed the conclusion of Hamilton and his colleagues on less direct evidence. Thomson, however, presents no evidence that these differences are inherited. What surprised Thomson was that 66 of the 130 deaths (51%) in the normal group were due to cardiovascular causes, a finding not irrelevant to Morrison and Morris's thesis.

Cruz-Coke (1959) measured the diastolic pressures in (*a*) 119 first-degree relatives of 35 hypertensive patients and (*b*) 59 first-degree relatives of 18 normotensive patients. His numbers were rather small, but the results as summarised in table IV are remarkably similar to those we have found: the arterial pressures are higher at all ages in the relatives of hypertensive propositi and the rates of rise of pressure are similar in the two sets of relatives. He also tabulated (table V) the mean pressures found twelve years before in 170 patients who afterwards became hypertensive (diastolic 105 mm. Hg or above) and 104 patients whose blood-pressure had always been normal (diastolic below 105 *mm.* Hg). The two series show corresponding differences and again show similar rates of rise with age.

Taken as a whole, these observations strongly suggest that what is inherited is not a tendency for the arterial pressure to rise more steeply with age, but a tendency

TABLE V—DIASTOLIC PRESSURES WHEN FIRST EXAMINED AT MEAN OF 12 YEARS PREVIOUSLY IN 170 SUBJECTS WHOSE PRESSURES REMAINED BELOW 105 DIASTOLIC AND IN 104 WHOSE PRESSURES SUBSEQUENTLY ROSE ABOVE 105 DIASTOLIC (CRUZ-COKE 1959)

Age (years)	Established normotensives		Previously normotensives (at present hypertensives)	
	No. of cases	Diastolic B.P. (mean and standard error)	No. of cases	Diastolic B.P. (mean and standard error)
30–34	62	72·9±0·95	18	84·0±2·93
35–39	45	75·4±1·25	28	87·7±1·68
40–44	30	77·5±1·62	18	88·5±2·65
45–49	18	76·6±1·61	18	90·4±2·62
50–54	8	84·4±4·23	13	95·0±4·05
55–59	7	85·0±2·30	9	95·0±3·05
	170		104	

The first two columns give the deaths from all causes and the subsequent ones those from causes which might have been associated with hypertension In those dying between ages 40–64, 27 4% of all deaths were due to diseases commonly associated with hypertension, of those dying from 65 upwards the percentage rises to 48 4 In the population sample of Hamilton and others (1954a) 37% of the males and 74% of the females in the age-group 65–69 had arterial pressures of 160 and over and the percentage rose in each succeeding age-group

Nor are they justified in concluding that a specific syndrome, essential hypertension, is closely associated with premature death in one or both parents Only 60% of Sobye's hypertensive propositi had one or both parents dying under the age of 65 In 168 patients now attending the hypertension clinic at the Radcliffe Infirmary 59% of fathers and 77% of the mothers who were dead died aged 65 and over

CLINICALLY A SPECIFIC DISEASE?

The Lancet (1959) said that the evidence that essential hypertension is a specific disease is more in keeping with its clinical behaviour Morrison and Morris claim to have identified by epidemiological methods a syndrome "which corresponds to the common clinical notion of 'essential hypertension', and this supports the hypothesis that essential hypertension is a specific disease entity"

To avoid the common fallacy of circular argument, we may now inquire whether there is any clinical evidence that essential hypertension behaves as a specific disease entity We know of none, but we know of much to suggest that it does not Two examples may suffice

Ayman and Pratt (1931) found that the incidence of early symptoms in their patients with essential hypertension was similar to those found in 50 psychoneurotic subjects with normal blood-pressure

Fishberg (1954) wrote "The clinical duration of essential hypertension varies between extremely wide limits There are instances in which an individual who 'has never been to a doctor' is suddenly seized on the street and expires before the arrival of the ambulance, at necropsy, a coronary occlusion or cerebral hæmorrhage is found, the origin of which in hypertension is revealed by the presence of cardiac hypertrophy and renal arteriosclerosis On the other hand, the hypertension may last for three or four decades and never do the subject any harm, until he finally dies of some disease having no relation to the hypertension These pictures constitute the extremes, and the vast majority of instances of essential hypertension fill all conceivable intermediary gaps between them."

Discussion

Having thus examined the evidence that essential hypertension is the manifestation of a single dominant gene, we find it wanting

The alternative hypothesis—that arterial pressure is inherited polygenically over the whole range, and that the inheritance is of the same kind and degree in the so-called normal range as in that characteristic of essential hypertension—is in general conformity with biological theory and with the facts of observation. Just as stature, the classical human example of polygenic inheritance, is the sum of a number of separate bones and tissues, so is the arterial pressure the resultant of a number of discrete components of the cardiovascular system. One need only mention the radii of different parts of the vascular sy -lengths of the vessels constituting

sition of the body fluids, the action of the heart, and the behaviour of the reflex mechanisms regulating arterial pressure To suppose that all this represents the effects of a specific enzyme formed by a specific gene would indeed be a revolutionary hypothesis and should require exceptionally cogent evidence in its favour

The evidence reviewed here proves to be more closely in accord with the idea of quantitative resemblance between hypertensive relatives, and thus with polygenic inheritance Perhaps the most important evidence for this hypothesis comes from the use of an age-and-sex-adjusted score for arterial pressures And since the use of this score has been criticised (*Lancet* 1959) a few words may be said in its defence

The method was introduced so that the behaviour of arterial pressure in the population could be studied quantitatively in terms of the quantity measured and not qualitatively in terms of arbitrary divisions into normal and hypertension The score "for any individual represents the number of mm Hg, in units of 5 mm., by which the observed pressure, systolic or diastolic, exceeds or falls short of the population average for that age and that sex, the scores being made fully comparable by further adjusting them to the corresponding value as at age 60 years" In a word, the scores are simply mean deviations, with additional allowance for the fact that variance also increases with age

On either hypothesis, single-gene or multifactorial, allowance for age must be made in some form or other Assuming a qualitative distinction, the appropriate method is to allow, as Sobye did, for increasing rate of manifestation On the other hand, assuming quantitative variation the appropriate method is the one we adopted, or some other method which is similar in principle It was shown that, applied to a population, the scores are in fact independent of sex and very nearly independent of age. The adjusted scores have also at least this empirical justification—that the measures of resemblance of subjects to fathers, mothers, brothers, sisters, sons, and daughters turn out not to differ significantly (Hamilton et al 1954c)

In their population studies Miall and Oldham (1958) calculated the regression coefficients for age-adjusted scores of individual classes of relatives on their propositi Significant differences were found in only 3—namely, the regression coefficients of diastolic scores for fathers, mothers and brothers on their female propositi, the rest of the 24 possible relationships were homogeneous The relatives are of course of very different mean ages and it would be rather surprising if such a correspondence were produced by chance by the use of a method inherently inappropriate to the material investigated

It is no part of our thesis that the method is perfect, but so far as we know no better has yet been devised To use some method of allowing for the effects of sex and age is accepted practice in biometrics Galton (1889) had to "transmute" his female heights to make them comparable with those of males to investigate the inheritance of stature Stocks (1930) used a device similar in principle in investigating resemblance in twins Analogous methods are universal in the treatment of intelligence-test scores in children

Using the age-and-sex-adjusted score and three methods of calculating the resemblance between first-degree relatives of hypertensive propositi Hamilton et al obtained by each method a regression coefficient of about 0 2 Miall and Oldham, investigating a true random sample of the populations of the Rhondda Fach and Vale of Glamorgan, obtained regression coefficients for relatives on propositi of 0 224±0 022 for systolic and 0 178±0 024 for diastolic scores, and these were independent of the blood-pressures of propositi The close similarity in the quantitative resemblance between first-degree relatives, whether their propositi were chosen because they presented as patients with essential hypertension or chosen at random from the population at large, is very strong evidence for the inheritance being quantitative and the same over the whole blood-pressure range This conclusion receives new support from the observations of Cruz-Coke from Chile, already described He gives the following mean scores for hypertensive propositi +53 1, for hypertensive relatives +10 0, for normotensive propositi −15 3, for normotensive relatives −4 0 The crude overall regression coefficient for relatives on propositi is then $\frac{10 + 4}{53\ 1 + 15\ 3} = 0\ 20$ The close similarity of this value to those obtained in a different continent and the other hemisphere is striking

The difficulty with regressions calculated on the basis of continuous variation is that very large numbers are needed before significant deviations from simple linear regressions can be detected Nevertheless the numbers are now fairly ample, and it does appear, as suggested, that a single regression of a little more than 0 2 accounts for the measures of resemblance to subjects of first-degree relatives of all kinds, and holds for all levels of arterial pressure from the highest to the lowest

In a critical appraisal of evidence it would be wrong to avoid voicing the doubt whether the resemblance found between blood-pressures of close relations can be accepted as valid evidence for inheritance Hogben (1957) and others have pointed out that close relatives tend to share not only a common inheritance but also a common environment Even the greater resemblance between the arterial pressures of identical than of non-identical twins demonstrated by Stocks (1930) and others may only mean that the former tend to live more nearly identical lives than the latter On this issue we have no conclusive evidence to offer Certain family resemblances undoubtedly have a genetic basis, and the resemblance in blood-pressure here summarised is most simply explained on a genetic basis

That environmental factors contribute materially to arterial pressure is suggested by the relatively small coefficient of resemblance—0 2 for blood-pressure as against 0 5 for stature (Pearson and Lee 1903) However, the much greater diurnal variability of blood-pressure than of height contributes appreciably to this disparity It is tempting to suppose that environmental factors are largely responsible for the rate and pattern of the rise of pressure with age Miall and Oldham (1958) found that for a given age and sex the arterial pressure was lower the greater the number of children, for those who had undertaken hard physical work and for those who ingested much salt In his repeated determinations after four years, Miall (1959) observed smaller rises in those with large families and in females who ate much salt, but not in those who did hard physical work Much thus remains to be done to define and measure environmental influences We cannot, however, leave this subject without referring to the very close accord between the mean values obtained for corresponding 5-year age-groups of populations so various as the inhabitants of Paddington (London), the mine-workers and agricultural workers of South Wales (Miall and Oldham 1955, 1958), farm workers of the United States (Gover 1948) and the tea workers of Assam, India (Wilson 1958) That genetic and environmental factors so various should have produced such similar mean end results is a phenomenon that challenges explanation

Finally, as to the nature of so-called essential hypertension We find the evidence that it represents a specific disease entity, a qualitative deviation from the norm, wanting in every particular This evidence is compatible, however, with the view that it represents a quantitative deviation to which inheritance makes a modest graded contribution Environmental factors as yet unspecified and unquantified are probably more important

The idea that this new quantitative hypothesis will inhibit research is one that we do not understand The history of new ideas does not suggest that they stop inquiry they stimulate it And if this new idea is more closely in accord with the facts than the old, it seems not impossible that the new idea may lead to a better understanding of the nature of the disease After all, the fruits of the old idea are scarcely impressive

Summary

Essential hypertension is looked at in two ways The old idea is that the disease is a specific entity, a qualitative deviation from the norm The new idea is that it is the consequence of a quantitative deviation from the norm

Controversy centres on the nature of the inheritance, the old idea drawing support from evidence favouring a single gene, the new idea from evidence favouring multifactorial or polygenic inheritance

The evidence for single-gene inheritance is unsatisfactory More probable is multifactorial inheritance as in stature, arterial pressure being inherited as a graded character over the whole range included in the conventional notations "normotension" and essential hypertension

The new hypothesis should stimulate inquiry If it is right, the inquiry may even be more rewarding

We are indebted to Dr W E Miall for the use of his data

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" Throughout an un-nursed life I've been sentimental about nurses, seeing them as angels of pity and comfort and always giving them my seat in trains I think now that I have been right about most of them But some are diminished by the enjoyment of bossy authority, some throw off a good deal of their kindness with their squeamishness, and some quarrel too openly and pettily in front of the patients, usually about infringements of territory All of them have sycophantic convulsions when the doctors are around (which the doctors contemplate too placidly) and all of them are slaves to routine, which begins at 5 30 A M with a cup of tea "—C H ROLPH, *New Statesman*, May 14, 1960, p 708 to higher pressures at all ages Such is in accord with our own casual or (as it is sometimes called) "clinical" experience, and with that of others The rate of rise and the pattern of rise is a highly individual experience and in individuals is largely independent of the first recorded pressure

Holmgren (1955) illustrated this by 19 examples of blood-pressure fluctuations over twenty to thirty-five years from age 31 upwards Bechgaard (1946) analysed the changes in arterial pressure of 192 men and 553 women with essential hypertension (blood-pressure 160/100 or 180 systolic upwards) over four to five years Comparing the first and last recorded pressures, 41% showed no change (within 20 mm), 22% a rise, and 37% a fall Between 140 and 200 mm systolic those with the lower pressures tended to show a rise and those with the higher pressures a fall at the second examination Above 200 mm there tended to be a rise at the second examination

TABLE VI—POPULATION SAMPLE (HAMILTON ET AL) SYSTOLIC PRESSURES OF SUBJECTS AGED 45–49

Age	Systolic pressures (mm Hg)			
	Less than 160	160 and above	Total	% 160 and above
Females				
45–49	103	11	114	9 6
50–54	92	39	131	29 8
55–59	67	41	108	38 0
Total	262	91	353	25 8
Males				
45–49	73	6	79	7 6
50–54	80	7	87	8 0
55–59	46	14	60	23 3
Total	199	27	226	11 9

CALCULATIONS BASED ON SUPPOSED GENE FREQUENCY

Both Sobye and Platt have calculated the frequency of the disease in the population and in the first-degree relatives of subjects with essential hypertension, on the assumption that a single dominant gene is concerned Platt's calculations were based on a disease frequency of 19–30%, Sobye concluded that "the disease occurs in the population at a frequency of about 30 to 40 per cent" It is reasonable to work in qualitative terms provided one is convinced that there is a qualitative distinction and that the population, at certain ages at least, can be divided into normals and hypertensives

If we assume that the population can be so divided, the first difficulty we meet is that the frequencies of affected and unaffected persons are different in the two sexes and in successive age-groups Table VI shows the percentages of those having pressures of 160 mm Hg and over in males and females of Hamilton's population sample To select a particular sex or age is purely arbitrary and critically determines any subsequent calculation

Even if we assume that a division into normal and affected is possible, a further difficulty arises The ratios between them calculated respectively on dominant-gene and multifactorial inheritance prove to be so alike that the data fail to differentiate between the two hypotheses

Given a single gene (or locus), and complete hereditary determination, the genetic correlation between first-degree relatives is 0 5, which corresponds to the proportion of genes they have in common The effect of dominance is to reduce this figure Assuming a gene frequency of 0 2, corresponding to Sobye's estimate, the reduction is not appreciable The figures become 0 44 for parent and child and 0 47 for sibs Assuming multifactorial inheritance the same correlation (or regression) of 0 5 would be found, but only of course if there were complete hereditary determination of blood-pressures

TABLE VII—PROPORTIONS OF AFFECTED INDIVIDUALS IN GENERAL POPULATION AND AMONG SIBS OF AFFECTED PROPOSITI GIVEN DIFFERENT GENE FREQUENCIES

Gene frequency	Proportion of affected in population	Proportion affected among sibs of propositi
5	10	54
10	19	58
15	28	62
20	36	66
25	44	70

Thus, if it is assumed that blood-pressure is completely determined hereditarily, the proportions of affected and unaffected will be nearly the same on the two hypotheses If it is not so assumed, the regressions and correlations have to be determined from the data How this is done will be discussed later We have previously shown (Hamilton et al 1954c) that ratios between affected and unaffected like those found by Sobye are compatible with a modest degree of multifactorial genetic resemblance Here we merely wish to point out that a choice between the two hypotheses cannot be made on calculations of supposed gene frequencies

Platt pointed out that if, as many people hold, hypertension affects 20–30% of the middle-aged population, giving a gene frequency for the dominant gene of 0 16 to 0 1, the observed proportion of hypertensive sibs should be 64–58%, close to what is observed This, however, is an insensitive test

In the limit, if the gene is rare, the expected percentage of affected sibs approaches 50 Table VII shows the expected proportions of affected sibs of affected propositi for gene frequencies of 5–25% corresponding to 10–44% of affected individuals in the population Platt wrote "if we use the systolic pressure of 150 as the dividing line, the proportion of hypertensive siblings is about 0 5" With 252 sibs the

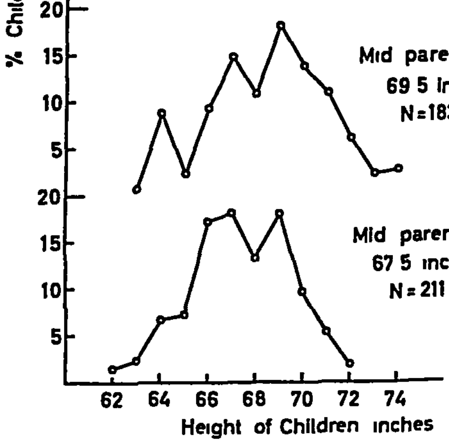

Fig 6—Frequency distribution of the heights of adult children derived from three groups of parents having mid-parent heights of 67½, 69½, and 71½ inches

The heights of children are given as 68 2 in and so on in the table not as here shown as 68 in and so on (Data from Francis Galton's *Natural Inheritance*, 1889, table XI) number Platt worked on, the 95% confidence limits are 53 and 65% affected, corresponding to gene frequencies of 4 and 19%, in the population at large the corresponding figures for affected persons are 7 and 34%

The observed figures of 59% quoted by Platt would fit almost any estimate of the frequency of the disease that has ever been proposed.

MORRISON AND MORRIS'S EVIDENCE

Morrison and Morris (1959) presented "data on the casual blood pressures and length of life of parents of a sample of drivers and conductors of London's buses"

They divided "the parents into those who died in middle age (40–64) and those living to old age (65 and over) on the assumption that this will give a crude subdivision into hypertensive and non-hypertensive groups, or at any rate, into groups with more hypertension and with less" They found that the frequency-distribution curve of blood-pressure of 90 drivers with one or both parents dead in middle age was bifid, while that of 96 drivers whose parents lived to 65 years and more was not. Referring to the first group they describe the curve as "obviously bimodal . with a break at about 160 mm. Hg between two groups of almost the same size Men forming the first peak (at about 140 mm) may reasonably be regarded as normotensive and those forming the second peak (at about 175 mm.) as hypertensive"

They further found that frequency-distribution curves of ages of death of parent were bifid for 53 fathers of hypertensive (160/95 mm. Hg or over) while not so for 121 fathers of normotensives (under 160/95) They concluded "that in a population sample, an apparently continuous blood-pressure distribution curve may mask a bimodal distribution and that this may be uncovered by means of the inheritance factor, by subdividing the sample according to the ages at death of the parents This reveals a special group of hypertensive subjects closely associated with premature death in one or both parents"

Two major criticisms may be made of Morrison and Morris's conclusions First they confuse irregularities of curves with bimodality If their curves are divided into the two constituent curves alleged to constitute their basic components, the results are to say the least bizarre

Fig 6 illustrates this point. It shows three frequency-distribution curves for the heights of children derived from parents whose mid-parent heights were 67 5, 69 5, and 71 5 in, taken from Galton's (1889) table XI from which he derived his concept of filial regression. In preparing this table Galton used a device to adjust female heights to those of males by multiplying them by 1 08 (transmuted female height) These curves show, as indeed do the complete data of table XI, that as parental stature increases, the frequency-distribution curves move to the right, so that the mean height of children is linearly related to that of parents

These curves (fig 6) show dips at 68 2 inches and some might interpret them as evidence of bimodality, exactly as they have interpreted the dips in frequency-distribution curves for arterial pressure They bear a superficial resemblance to some of the curves in fig 1, but since none of the other four frequency distributions of table XI show similar dips, they resemble Hamilton's more than Sobye's curves

No student of the genetics of stature has yet attached significance to these dips That stature is distributed normally for large numbers is illustrated by the curve for the stature of 91,163 recruits to the British Army measured during the last war (fig 7)

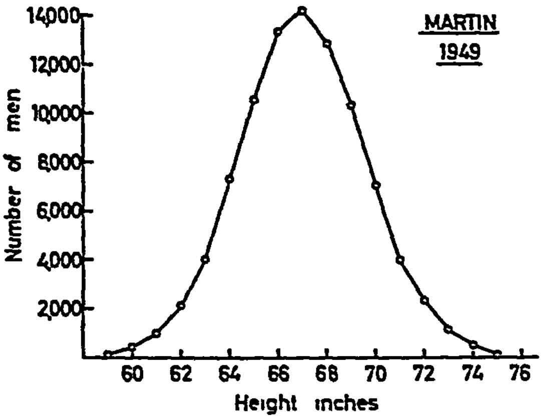

Fig 7—Frequency distribution of height in 91 163 recruits to the British Army
(Data from Martin 1949)

Second their assumption that a division of deaths at age 65 divides the population into those with and without hypertension is far from the truth.

Table VIII is compiled from the Registrar General's returns for England and Wales for 1935, a year chosen to be representative of a period in which might be expected to die the parents of busdrivers aged 45–60 examined by Morrison and Morris

TABLE VIII—CAUSES OF DEATH AT DIFFERENT AGE PERIODS, ENGLAND AND WALES 1935

Age-group	Total		Cerebral hæmorrhage so returned and apoplexy lesion unstated cerebral hæmorrhage and apoplexy 82(a) 1 & 2		Cerebral embolism and thrombosis 82(b)		Diseases of the myocardium 93		Diseases of the coronary arteries 94		Other diseases of the heart 95		Arterio-sclerosis 97		Nephritis 130 132		Total deaths	Total cardio-vascular (M & F) combined	Proportion of total
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F			
40	7181	6675	94	142	25	36	298	253	162	39	52	74	45	41	244	284	13,856	1789	12·91%
45	10,481	8640	229	298	44	73	605	519	375	93	106	112	109	99	360	418	19,121	3440	17·97%
50	14 434	11,571	417	588	108	114	1147	963	733	179	187	174	303	277	649	529	26,005	6368	24·49%
55	19,301	15,219	733	873	199	192	2039	1619	1069	328	280	263	669	488	768	713	34,520	10,233	29·64%
60	24 633	19,867	1082	1227	314	356	3376	2884	1369	534	375	426	1177	928	1072	923	44,500	16,043	36·05%
Total 40–60	76 030	61,972	2555	3128	690	771	7465	6238	3708	1173	1000	1049	2303	1833	3093	2867	138,002	37,873	27·44%
65	28,748	24,685	1436	1667	518	568	4948	4554	1507	764	537	560	1858	1399	1170	1087	53 453	22,575	42 25%
70	30,278	29,511	1683	1948	614	709	6354	6695	1405	839	557	747	2430	2152	1207	1167	59 789	28,507	47·68%
75	26,503	29,658	1371	1874	589	836	6497	7808	924	708	527	713	2376	2387	933	995	56 161	28,538	50 82%
80	26,101	39,952	1011	1962	526	1074	7295	11,913	576	553	434	824	2448	3269	732	909	66 053	33,526	50·76%
Total 65–80	111,630	123,806	5501	7451	2247	3187	25,094	30,970	4412	2864	2055	2844	9112	9207	4042	4158	235,436	113,146	48·06%
Total 40–80	187,660	185,778	8056	10,579	2937	3958	32,559	37,208	8120	4037	3055	3893	11,415	11,040	7135	7025	373,438	151,024	40·42%

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Fishberg (1954) wrote " The clinical duration of essential hypertension varies between extremely wide limits There are instances in which an individual who ' has never been to a doctor ' is suddenly seized on the street and expires before the arrival of the ambulance, at necropsy, a coronary occlusion or cerebral hæmorrhage is found, the origin of which in hypertension is revealed by the presence of cardiac hypertrophy and renal arteriosclerosis On the other hand, the hypertension may last for three or four decades and never do the subject any harm, until he finally dies of some disease having no relation to the hypertension These pictures constitute the extremes, and the vast majority of instances of essential hypertension fill all conceivable intermediary gaps between them "

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The method was introduced so that the behaviour of arterial pressure in the population could be studied quantitatively in terms of the quantity measured and not qualitatively in terms of arbitrary divisions into normal and hypertension The score " for any individual represents the number of mm Hg, in units of 5 mm., by which the observed pressure, systolic or diastolic, exceeds or falls short of the population average for that age and that sex, the scores being made fully comparable by further adjusting them to the corresponding value as at age 60 years " In a word, the scores are simply mean deviations, with additional allowance for the fact that variance also increases with age

On either hypothesis, single-gene or multifactorial, allowance for age must be made in some form or other Assuming a qualitative distinction, the appropriate method is to allow, as Sobye did, for increasing rate of manifestation On the other hand, assuming quantitative variation the appropriate method is the one we adopted, or some other method which is similar in principle It was shown that, applied to a population, the scores are in fact independent of sex and very nearly independent of age The adjusted scores have also at least this empirical justification—that the measures of resemblance of subjects to fathers, mothers, brothers, sisters, sons, and daughters turn out not to differ significantly (Hamilton et al 1954c)

In their population studies Miall and Oldham (1958) calculated the regression coefficients for age-adjusted scores of individual classes of relatives on their propositi Significant differences were found in only 3—namely, the regression coefficients of diastolic scores for fathers, mothers and brothers on their female propositi, the rest of the 24 possible relationships were homogeneous The relatives are of course of very different mean ages and it would be rather surprising if such a correspondence were produced by chance by the use of a method inherently inappropriate to the material investigated

It is no part of our thesis that the method is perfect, but so far as we know no better has yet been devised To use some method of allowing for the effects of sex and age is accepted practice in biometrics Galton (1889) had to " transmute " his female heights to make them comparable with those of males to investigate the inheritance of stature Stocks (1930) used a device similar in principle in investigating resemblance in twins Analogous methods are universal in the treatment of intelligence-test scores in children

Using the age-and-sex-adjusted score and three methods of calculating the resemblance between first-degree relatives of hypertensive propositi Hamilton et al obtained by each method a regression coefficient of about 0 2 Miall and Oldham, investigating a true random sample of the populations of the Rhondda Fach and Vale of Glamorgan, obtained regression coefficients for relatives on propositi of 0 224±0 022 for systolic and 0 178±0 024 for diastolic scores, and these were independent of the blood-pressures of propositi The close similarity in the quantitative resemblance between first-degree relatives, whether their propositi were chosen because they presented as patients with essential hypertension or chosen at random from the population at large, is very strong evidence for the inheritance being quantitative and the same over the whole blood-pressure range This conclusion receives new support from the observations of Cruz-Coke from Chile, already described He gives the following mean scores for hypertensive propositi +53 1, for hypertensive relatives −10 0, for normotensive propositi −15 3, for normotensive relatives −4 0 The crude overall regression coefficient for relatives on propositi is then $\frac{10 + 4}{53\ 1 - 15\ 3} = 0\ 20$ The close similarity of this value to those obtained in a different continent and the other hemisphere is striking

The difficulty with regressions calculated on the basis of continuous variation is that very large numbers are needed before significant deviations from simple linear regressions can be detected Nevertheless the numbers are now fairly ample, and it does appear, as suggested, that a single regression of a little more than 0 2 accounts for the measures of resemblance to subjects of first-degree relatives of all kinds, and holds for all levels of arterial pressure from the highest to the lowest

In a critical appraisal of evidence it would be wrong to avoid voicing the doubt whether the resemblance found between blood-pressures of close relations can be accepted as valid evidence for inheritance Hogben (1957) and others have pointed out that close relatives tend to share not only a common inheritance but also a common environment Even the greater resemblance between the arterial pressures of identical than of non-identical twins demonstrated by Stocks (1930) and others may only mean that the former tend to live more nearly identical lives than the latter On this issue we have no conclusive evidence to offer Certain family resemblances undoubtedly have a genetic basis, and the resemblance in blood-pressure here summarised is most simply explained on a genetic basis

That environmental factors contribute materially to arterial pressure is suggested by the relatively small coefficient of resemblance—0 2 for blood-pressure as against 0 5 for stature (Pearson and Lee 1903) However, the much greater diurnal variability of blood-pressure than of height contributes appreciably to this disparity It is tempting to suppose that environmental factors are largely responsible for the rate and pattern of the rise of pressure with age Miall and Oldham (1958) found that for a given age and sex the arterial pressure was lower the greater the number of children, for those who had undertaken hard physical work and for those who ingested much salt In his repeated determinations after four years, Miall (1959) observed smaller rises in those with large families and in females who ate much salt, but not in those who did hard physical work Much thus remains to be done to define and measure environmental influences We cannot, however, leave this subject without referring to the very close accord between the mean values obtained for corresponding 5-year age-groups of populations so various as the inhabitants of Paddington (London), the mine-workers and agricultural workers of South Wales (Miall and Oldham 1955, 1958), farm workers of the United States (Gover 1948) and the tea workers of Assam, India (Wilson 1958) That genetic and environmental factors so various should have produced such similar mean end results is a phenomenon that challenges explanation

Finally, as to the nature of so-called essential hypertension We find the evidence that it represents a specific disease entity, a qualitative deviation from the norm, wanting in every particular This evidence is compatible, however, with the view that it represents a quantitative deviation to which inheritance makes a modest graded contribution Environmental factors as yet unspecified and unquantified are probably more important

The idea that this new quantitative hypothesis will inhibit research is one that we do not understand The history of new ideas does not suggest that they stop inquiry they stimulate it And if this new idea is more closely in accord with the facts than the old it seems not impossible that the new idea may lead to a better understanding of the nature of the disease After all, the fruits of the old idea are scarcely impressive

Summary

Essential hypertension is looked at in two ways The old idea is that the disease is a specific entity, a qualitative deviation from the norm The new idea is that it is the consequence of a quantitative deviation from the norm

Controversy centres on the nature of the inheritance, the old idea drawing support from evidence favouring a single gene, the new idea from evidence favouring multifactorial or polygenic inheritance.

The evidence for single-gene inheritance is unsatisfactory More probable is multifactorial inheritance as in stature, arterial pressure being inherited as a graded character over the whole range included in the conventional notations "normotension" and essential hypertension

The new hypothesis should stimulate inquiry If it is right, the inquiry may even be more rewarding

We are indebted to Dr W E Miall for the use of his data

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"Throughout an un-nursed life I've been sentimental about nurses, seeing them as angels of pity and comfort and always giving them my seat in trains I think now that I have been right about most of them But some are diminished by the enjoyment of bossy authority, some throw off a good deal of their kindness with their squeamishness, and some quarrel too openly and pettily in front of the patients, usually about infringements of territory All of them have sycophantic convulsions when the doctors are around (which the doctors contemplate too placidly) and all of them are slaves to routine, which begins at 5.30 A M with a cup of tea"—C H ROLPH, *New Statesman*, May 14, 1960, p 708

REDUCTION OF INTRACRANIAL PRESSURE WITH HYPERTONIC UREA

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INCREASED intracranial pressure is one of the commonest and most troublesome problems confronting neurological surgeons. It is responsible for many of the symptoms of expanding intracranial lesions, for much difficulty encountered at operations, for complicated convalescence, and for incomplete recovery. The "tight" brain is well known: when the dura is opened the brain bulges, and, unless the pressure can be relieved, it may burst. Short of this, increased pressure limits access to deepseated lesions, and it may be responsible for unnecessary damage to the brain by vigorous retraction.

Among the measures taken to reduce the pressure are elevation of the head (which lowers the venous pressure within the cranium), removal of cerebrospinal fluid (C.S.F.) by ventricular puncture (or less often by lumbar puncture), and "dehydration" by intravenous infusion of hypertonic solutions such as sodium chloride, glucose, or sucrose. More recently anæsthetic techniques have contributed—e.g., by induced hypothermia, the use of ganglioplegic drugs, or "controlled" respiration of the curarised patient. But occasionally, for one reason or another, none of these methods is adequate. This report is concerned with the use of another substance, urea, which seems superior to and more generally effective than any other in reducing intracranial pressure. It was recommended by Javid (1958), whose account should be read by all interested in the subject. Our experience of its use in 129 patients in the United Oxford Hospitals during the past eleven months is in general agreement with his findings.

Javid records that Fremont-Smith and Forbes (1927) observed a remarkable reduction in the C.S.F. pressure of cats after the intraperitoneal injection of hypertonic urea. They stated that "*its lack of toxicity and its ready elimination by normal kidneys suggest the possibility of a clinical application*." But this suggestion lay fallow for nearly a quarter of a century until Smythe et al. (1950) found that, on an equiosmolar basis, urea was more effective than glucose in reducing the C.S.F. pressure *in monkeys*.

In 1954, Javid and Settlage used urea for the first time in man, and two years later (1956) they reported encouraging results in 21 patients. In 1958, Javid described with more confidence the results in 300 patients, taking the view that "urea is a highly useful and safe agent for reducing intracranial and intraocular pressure. It is far superior in every respect to all other agents commonly used for this purpose." He found that doses of 1·0–1·5 g. per kg. body-weight were effective and well tolerated, and that 10% invert sugar solution was the best agent for dissolving the urea crystals. With 30% urea in 10% invert sugar he observed no hæmolysis, as in experimental animals which had had urea with other solutes.

Method

We have largely followed the method of Javid (1958) and have given most of our patients 1·0–1·5 g. urea per kg. body-weight intravenously as a 30% solution in 10% invert sugar.

The urea solutions we used for these cases were prepared under the direction of Mr. W. Trillwood, chief pharmacist to the United Oxford Hospitals.

The urea was made up as a 60% solution in distilled water, and sterilised by filtration. Because the solution is not stable indefinitely, it was stored in sterile bottles at 2–5°C to reduce the rate of decomposition to a minimum. It should not be kept longer than twenty-one days. Just before use the solution was allowed to come to room temperature and was mixed with an equal volume of sterile 20% invert sugar solution.*

The infusion is given by gravity into a vein in the arm or leg. When a protracted effect is required, we have found that the optimal rate of administration is about 60 drops per minute, as Javid recommended. The effect on the intracranial pressure is seen within fifteen to twenty minutes of starting the infusion, and an adequate reduction in pressure persists for four to eight hours.

But we have also given the infusion much more rapidly without apparent ill effects. When used for craniotomies, where a greater reduction in brain bulk is desired for a shorter time, we have given the total dose within fifteen or twenty minutes. We find it convenient to begin the infusion at the same time as the induction of anæsthesia.

Effects of Urea Infusion

At Operation

Reduction in brain bulk is the most notable effect. When, for instance, a frontal osteoplastic flap is raised, as for the exposure of a pituitary tumour or basal aneurysm, the dura falls away from the bone edges at the margins of the opening, and its whole surface is crinkled. When opened, the brain likewise falls away from the dura, and a space of as much as 2 cm. may be left between the frontal lobe and the posterior surface of the frontal sinus. Even in cases of expanding lesions within the brain, with gross increase in intracranial pressure, the dura is quite slack, and since using urea we have not had to tap the opposite ventricle before opening the dura. The benefits are obvious: access to the lesion is improved, much less retraction is required as a result, and the brain is damaged less. Recovery from operation is thus more rapid and complete, and everyone concerned with these patients has been impressed by their easy convalescence. To see a patient sitting up in bed, with no œdema of the eyelids, and doing a crossword puzzle, the morning after the removal of a massive bifrontal meningioma together with its attachment to the falx and sagittal sinus, is a new experience in neurosurgery.

Bleeding.—Although urea makes operating easier and safer, paradoxically bleeding is increased in the early stages of operation. Two factors seem to be responsible. First and obvious is that, as the dura falls away from the skull when burr-holes and saw cuts are made, there is more venous bleeding from the dura in the space between it and the bone. This can be checked by pressure with gelatin foam, but we usually hitch up the dura to the pericranium at four or five points around the craniotomy, either at the beginning, or more often at the end, of the intradural procedure.

Secondly, more bleeding from small vessels in the scalp, dura, and brain seems to arise in the first twenty minutes or half-hour of operation than later. This is mostly arterial oozing, and is more of a nuisance than a danger. We have not found any defect in the hæmostatic mechanism, and we think that this kind of bleeding may be a result of the transient increase in blood-volume caused by the infusion of a hypertonic solution. This problem is being investigated further.

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* *A much more stable form of urea for intravenous use is now available commercially from Baxter Laboratories Ltd., 26, Great Tower Street, London, E.C.3.*

No postoperative clots have formed after urea has been used This is surprising, considering the factors mentioned above, and the slackness of the brain at the end of operation

Lumbar C S F Pressure

In a few patients we have studied the response of the lumbar C S F pressure to urea administration Although lumbar pressure is not always an accurate index of intracranial pressure, when the intracranial pressure is high the lumbar pressure is usually also raised The effects of urea on the intracranial pressure should be reflected in a reduction of the pressure as determined by lumbar puncture A typical response is shown in fig 1 In this case an initial pressure of 180 mm water dropped to −80 mm at the height of diuresis two and a half hours after starting the infusion of urea But the temporal relation between diuresis and fall in pressure is often less precise (fig 2) (Indeed, to study the possible causal relation between pressure fall and diuresis, Javid and Anderson [1959] gave various hypertonic solutions, including urea, to monkeys before and after bilateral nephrectomy After nephrectomy they found the fall in C S F pressure was greater and better sustained than before nephrectomy After excluding the relevance of the associated urinary diuresis Javid [1958] implicated the blood-C S F barrier)

The patient whose responses are recorded in fig 1 was conscious throughout His only significant subjective impressions were dryness of the mouth, which began with the diuresis, and mild frontal and occipital headache when his lumbar C S F pressure was less than atmospheric

Biochemical Changes

Diuresis begins shortly after the introduction of the urea, is at a maximum between half and three hours later, and continues at a diminishing rate for three to nine hours As large quantities of urine may be excreted we insert a catheter into the bladder at the beginning of the infusion, and then release it hourly to avoid distension of the bladder

The blood-urea level rises from the beginning of the infusion, and reaches its maximum at the end of the infusion It falls slowly from that time, reaching normal in twenty to thirty hours Values as high as 540 mg per 100 ml have been seen, without untoward clinical effects But, because urea retention may be harmful, intravenous urea should not be given to patients with impaired renal function

Toxicity

We have seen no major toxic effects During the urea infusion 5 patients had rigors, but these ceased shortly after the infusion was stopped In 3 cases we attributed the rigor to the fact that we had not allowed the solution to come to room temperature and because the rate of infusion was too rapid In the other 2 the reaction was probably due to decomposition of the urea solution through age or improper storage None of them showed any untoward result, and in particular there was no evidence of intravascular hæmolysis

In a few arteriosclerotic patients Javid (1958) noted that the vein became prominent, distal to the needle, when a vein of the foot was used We have noted similar local reactions, and occasionally in younger patients also In some the vein has become very red and swollen both proximal and distal to the site of infusion and in the conscious patient this may be painful But the reaction has been shortlived, and has never progressed to thrombosis of the superficial and deep leg veins as in one of Javid's cases

Local reactions were less frequent in the arm than the leg With the patient recumbent slight elevation of the limb reduces the frequency of local venous irritation The limb should be elevated only slightly—say by placing it on a pillow—so that at the point of entry of the needle the venous pressure is atmospheric or only slightly above The proximal veins are then not fully distended The flow is more rapid, and dilution of the urea by blood from other tributaries is more prompt

Constancy of Effects and Diverse Uses

We have used intravenous urea in 102 intracranial operations for various pathological processes

Glioma	26
Meningioma	12
Aneurysm	7
Lesions in and near the sella	14
Intracranial hæmatoma	3
Abscess	5
Trigeminal-root section	15
Posterior-fossa lesions	8
Miscellaneous	12

All cases showed obvious benefit, although this was sometimes more dramatic than others Thus, the effect was less obvious in posterior-fossa lesions causing hydrocephalus than it was in lesions of the cerebral hemispheres, but, as one can almost always reduce the pressure by tapping a dilated ventricle, the need for urea is less in posterior-fossa tumours

Apart from its use during operation, we think urea may have other important uses One of these may best be illustrated

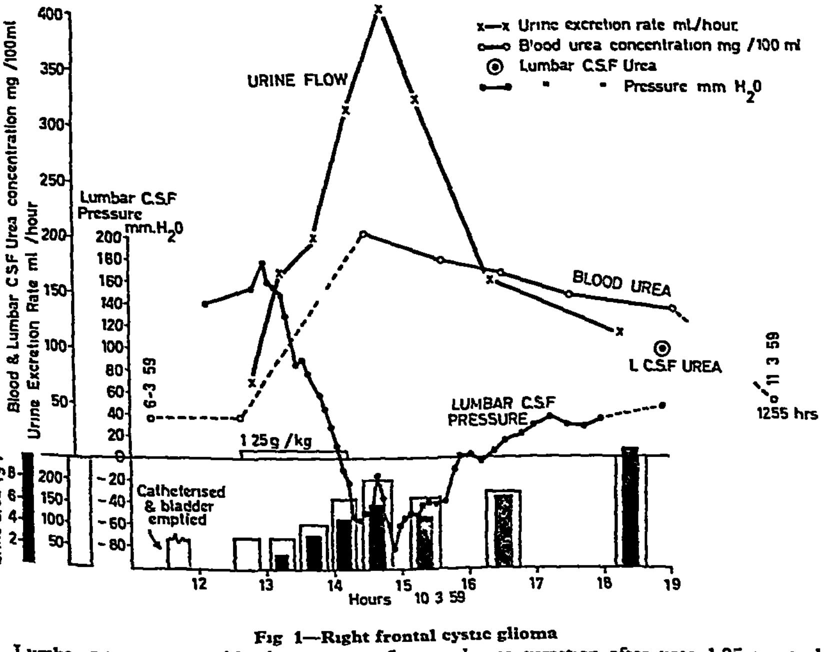

Fig 1—Right frontal cystic glioma

Lumbar C S F pressure, blood-urea, urine-flow, and urea excretion after urea 1 25 g per kg body-weight by intravenous infusion

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Comparison with Pressure-reduction by Controlled Respiration

We have too little experience of controlled respiration to make a useful comparison, but our impression from 5 recent cases is that controlled respiration considerably reduces the vascularity of the scalp, dura, and brain, and in this respect is superior to urea Its pressure-reducing effect, however, is much less than that of urea In 11 further cases we have combined the two procedures This may indeed be the ideal combination, and there seems to be no theoretical or practical objection

Mechanism of Action

Any theory of mechanism must explain the following

1 The reduction in C S F pressure, and, when the skull is opened, the reduction in volume of the intracranial contents

2 Why urea, on an equiosmolar basis, produces a more protracted and profound effect than other hypertonic agents

3 The absence of a secondary rise in pressure (a rebound phenomenon), such as often occurs after giving sodium chloride

Weed and McKibben (1919) argued that hypertonic agents generally act by reducing principally the brain bulk rather than the C S F volume or the intracranial blood-volume They suggested that the brain bulk is diminished by water loss as long as the concentration of the agent is higher in the blood than in the brain there is an osmotic gradient favouring the passage of water from brain to blood The less readily a substance passes from blood to brain the longer will this osmotic gradient be maintained, and the greater will be the transfer of water If a substance enters the brain much less readily than it enters other soft tissues (i e , a blood-brain barrier effect), then, when given intravenously in hypertonic solution, it will selectively dehydrate the brain

The reduction in brain bulk is obviously much greater than that of other soft tissues of comparable water content, and we think that a barrier to the entry of urea into the brain best explains our clinical observations We suggest that urea is more effective than other agents because it enters the brain more slowly

Davson (1956) in a discussion of the mode of action of hypertonic agents, emphasises the significance of a barrier effect, but he does not distinguish between the relative importance of the blood-brain barrier on the one hand and the blood-C S F barrier on the other When considering specifically the mode of action of hypertonic urea, Javid (1958) implicates the blood-C S F barrier

We feel that the following clinical observations support Weed and McKibben's belief (1919) that the blood-brain exchanges are relatively more important

1 Urea is less effective in patients with much hydrocephalus, in whom there is relatively more C S F and a smaller brain-volume than normal

2 Urea is effective in reducing brain bulk during craniotomy in patients with diffuse and severe cerebral swelling due to trauma At the time of giving urea little intracranial C S F could have been available for reabsorption

3 If urea is given during craniotomy to patients in whom continuous ventricular drainage has first been established, then the volume of the intracranial contents is reduced very much further

Little is known about the rate of entry of urea into the brain relative to its entry into other soft tissues Only two in-vivo studies have been reported

That by Riser et al (1938) suggests that urea diffuses into the brain almost as rapidly as it does into muscle, and that at high urea levels the urea concentration in both brain and muscle approaches that of plasma Conway and Fitzgerald (1942) on the other hand, provided more definite evidence in favour of a barrier to urea They showed that urea enters the brain much more slowly than it enters muscle Both groups of investigators found that at equilibrium at normal urea levels the brain contains significantly less urea than the plasma But because in both studies the observations were few, such experiments must be repeated

In-vivo rather than in-vitro studies are necessary as the blood-brain barrier presumably depends upon the integrity of the normal in-vivo anatomical relation between plasma in the capillary lumen and the brain substance Thus, Coxon's report (1957) on the free entry of urea into isolated guineapig brain slices is not relevant to this study

As to the nature of the barrier, a simple physical obstruction to free diffusion is one possibility Such an obstructive barrier would almost certainly retard the exit of urea from the brain as much as it would delay the entry Thus, as urea is excreted by the kidneys and the plasma level falls, one would expect the brain-urea concentration to exceed that of the plasma-urea until equilibrium is again reached at normal urea levels During this interval the osmotic gradient would favour the passage of water from plasma to brain, producing a rebound rise in pressure We have not seen such a secondary rise in pressure after giving hypertonic urea to our patients, nor have we seen this in the few cases in which we have made extended manometric studies More probably the barrier to urea is an energy-consuming metabolic process, and urea is actively "pumped out" of the brain as the plasma level falls

The mechanism requires further study, for it has obvious importance, theoretical and practical We are now engaged in experiments designed to test this barrier hypothesis

Summary

In 129 neurosurgical patients intravenous urea was used to reduce the intracranial pressure The main effect was a decrease in brain bulk, which made operation easier and safer Although arterial oozing was often increased in the early stages of operation, this was more of a nuisance than a danger The fall in intracranial pressure was measurable at lumbar puncture

No major toxic effects arose Local reactions were noted in the vein used, but they never progressed to thrombosis The blood-urea level rose and diuresis began shortly after the infusion was started, hence urea should not be given to patients with impaired renal function

Apart from its use during brain operations urea may serve (1) to tide over a comatose patient until he can be got to a neurosurgical centre, (2) for treating "the second-day slump", (3) for cases of acute head injury or tuberculous meningitis in which the intracranial pressure is high, and (4) for relieving benign intracranial hypertension

The most likely mechanism of the reduction of intracranial pressure is by means of a blood-brain barrier to urea

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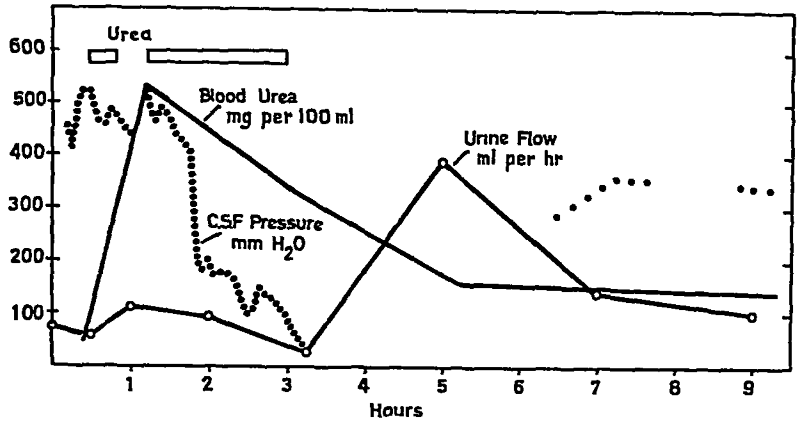

Fig 2—Tuberculous meningitis

Lumbar C S F pressure, blood-urea, and urine-flow after urea 1 25 g per kg body-weight by intravenous infusion

by observations on a patient who proved to have a right frontal glioma He was admitted in coma, which had come on over thirty-six hours, and which had been deepened by exploratory burr-holes and aspirations He was then given intravenous urea, and within an hour and a half he was conscious and rational enough to cooperate in a full examination This pointed to the site of the lesion, which was then confirmed by angiography Thus, urea may usefully tide over a comatose patient until he can be got into neurosurgical hands, and indeed it may keep him going until operation can be arranged We have seen its benefit in 6 such cases Incidentally its effect lasts longer than that of other hypertonic solutions, and there is little of the "rebound" in pressure which often follows their use Thus, it might be used safely to prepare a patient for an ambulance journey from an outlying hospital to a neurosurgical centre

We have also used urea with dramatic effect in what our American colleagues call "the second-day slump" This happens in patients who are very well the day after craniotomy On the second day they become drowsy—sometimes comatose—and may develop neurological signs referable to the operation site (e g , hemiplegia or aphasia) The safe assumption is that a clot has accumulated This requires re-elevation of the bone-flap, and inspection of the operative site, but more often than not, no significant clot is found, the brain only appearing slightly swollen Such patients usually recover, but they can cause much anxiety In one such case when we tried intravenous urea, the patient became fully conscious and was without neurological deficit by the time the infusion was completed This state lasted for about eighteen hours, when he again became drowsy This time a half dose of urea was given, again with prompt recovery, which persisted

Head injuries—We have used urea in 22 cases of acute head injury in which the brain was "tight", after sizeable clots had been excluded by multiple burr-holes or craniotomy Once, at operation, the effect was as dramatic as described above, but the patient's condition did not improve correspondingly He did make a good recovery eventually, although it would be difficult to deny that he might have done so without urea This is a common difficulty in evaluating the "medical" treatment of head injuries—e g , with hypothermia or dehydration But if the intracranial pressure is known to be high, if sizeable clots have been excluded, and if urea is known to be safe (as we believe it to be in these circumstances), it seems reasonable to try it

Tuberculous meningitis—We have used urea in 3 cases of tuberculous meningitis in which increased intracranial pressure seemed to demand some kind of decompression procedure

Fig 2 records its effect in a 23-year-old woman who was admitted to the tuberculous-meningitis unit with a proven infection The striking clinical feature was bilateral papillœdema Treatment with intrathecal streptomycin was started, but she continued to have severe headache, the lumbar C S F pressure rose, and the papillœdema increased An air-encephalogram indicated obstruction by basal exudate, hence a course of intrathecal tuberculin was started While her general condition remained the same, the C S F pressure continued to rise to about 500 mm water, fresh retinal hæmorrhages appeared, and the visual acuity, which had been J 1 bilaterally, dropped to J 16 in the right eye and J 2 in the left. At this stage urea was given intravenously, and then it was continued orally (vide infra) for forty-eight hours The lumbar pressure fell, no further changes appeared in the retinæ, and the visual acuity returned to normal A week later the lumbar pressure again rose to 500 mm , but it was reduced to normal with urea given by mouth The patient later recovered satisfactorily, with normal vision

Urea was beneficial in the 2nd patient, but not in the 3rd, who was critically ill with tuberculous meningitis, and showed evidence of ventricular and subarachnoid bleeding

Benign intracranial hypertension (otitic hydrocephalus)—In 2 patients with this affection urea has brought about a prompt and striking reduction in the lumbar C S F pressure, but, as they were both in good general condition and had only moderate papillœdema with no reduction in visual acuity, we did not consider further treatment necessary Urea might be useful in patients with pronounced papillœdema and failing vision, for whom surgical decompression is usually advised In such cases, the oral route might be preferable to repeated intravenous infusions Javid (1958) has shown that urea is effective when given by mouth in doses comparable to those given intravenously Urea crystals can be dissolved in water We have found the following mixture reasonably palatable urea, 300 g , simple syrup, 150 ml , syrup of orange, 150 ml , and water to 1000 ml Such solutions should be stored at 2–8°C and should not be used after seven days from their preparation The total daily dose of 1–1 5 g per kg body-weight is divided into three and taken eight-hourly It has an unpleasant taste, and sometimes causes vomiting, which if persistent may necessitate discontinuing treatment by this route But when urea can be taken by mouth the patient is also spared discomfort from local reaction in the vein used for infusion Furthermore, in the conscious patient the rapid reduction in pressure accompanying intravenous infusion may cause much headache

Contraindications

As noted above, urea should not be used in patients with impaired renal function On admission we examine the urine and determine the blood-urea, and, if these are normal, we have no hesitation in using urea The youngest patient was two years old, and the oldest seventy-two

Because the tendency to increased bleeding already mentioned may contraindicate the use of urea, we doubt whether it has a place in the treatment of acute subarachnoid or intracerebral hæmorrhage, except as an immediate preoperative measure Until more is known about its mode of action and effects, we advise against its indiscriminate use in acute head injuries in which the pathology is not certainly known

Comparison with Pressure-reduction by Controlled Respiration

We have too little experience of controlled respiration to make a useful comparison but our impression from 5 recent cases is that controlled respiration considerably reduces the vascularity of the scalp, dura and brain, and in this respect is superior to urea Its pressure-reducing effect, however, is much less than that of urea In 11 further cases we have combined the two procedures This may indeed be the ideal combination, and there seems to be no theoretical or practical objection

Mechanism of Action

Any theory of mechanism must explain the following

1 The reduction in C.S.F. pressure, and, when the skull is opened, the reduction in volume of the intracranial contents

2 Why urea, on an equiosmolar basis, produces a more protracted and profound effect than other hypertonic agents

3 The absence of a secondary rise in pressure (a rebound phenomenon), such as often occurs after giving sodium chloride

Weed and McKibben (1919) argued that hypertonic agents generally act by reducing principally the brain bulk rather than the C.S.F. volume or the intracranial blood-volume They suggested that the brain bulk is diminished by water loss as long as the concentration of the agent is higher in the blood than in the brain there is an osmotic gradient favouring the passage of water from brain to blood The less readily a substance passes from blood to brain the longer will this osmotic gradient be maintained, and the greater will be the transfer of water If a substance enters the brain much less readily than it enters other soft tissues (i e., a blood-brain barrier effect), then, when given intravenously in hypertonic solution, it will selectively dehydrate the brain

The reduction in brain bulk is obviously much greater than that of other soft tissues of comparable water content, and we think that a barrier to the entry of urea into the brain best explains our clinical observations We suggest that urea is more effective than other agents because it enters the brain more slowly

Davson (1956) in a discussion of the mode of action of hypertonic agents, emphasises the significance of a barrier effect, but he does not distinguish between the relative importance of the blood-brain barrier on the one hand and the blood-C.S.F. barrier on the other When considering specifically the mode of action of hypertonic urea, Javid (1958) implicates the blood-C.S.F. barrier

We feel that the following clinical observations support Weed and McKibben's belief (1919) that the blood-brain exchanges are relatively more important

1 Urea is less effective in patients with much hydrocephalus, in whom there is relatively more C.S.F. and a smaller brain-volume than normal

2 Urea is effective in reducing brain bulk during craniotomy in patients with diffuse and severe cerebral swelling due to trauma At the time of giving urea little intracranial C.S.F. could have been available for reabsorption

3 If urea is given during craniotomy to patients in whom continuous ventricular drainage has first been established, then the volume of the intracranial contents is reduced very much further

Little is known about the rate of entry of urea into the brain relative to its entry into other soft tissues Only two in-vivo studies have been reported

That by Riser et al (1938) suggests that urea diffuses into the brain almost as rapidly as it does into muscle, and that at urea levels the urea concentration in both brain and muscle approaches that of plasma Conway and Fitzgerald (1942) on the other hand, provided more definite evidence in favour of a barrier to urea They showed that urea enters the brain much more slowly than it enters muscle Both groups of investigators found that at equilibrium at normal urea levels the brain contains significantly less urea than the plasma But because in both studies the observations were few, such experiments must be repeated

In-vivo rather than in-vitro studies are necessary as the blood-brain barrier presumably depends upon the integrity of the normal in-vivo anatomical relation between plasma in the capillary lumen and the brain substance Thus, Coxon's report (1957) on the free entry of urea into isolated guineapig brain slices is not relevant to this study

As to the nature of the barrier, a simple physical obstruction to free diffusion is one possibility Such an obstructive barrier would almost certainly retard the exit of urea from the brain as much as it would delay the entry Thus, as urea is excreted by the kidneys and the plasma level falls, one would expect the brain-urea concentration to exceed that of the plasma-urea until equilibrium is again reached at normal urea levels During this interval the osmotic gradient would favour the passage of water from plasma to brain, producing a rebound rise in pressure We have not seen such a secondary rise in pressure after giving hypertonic urea to our patients, nor have we seen this in the few cases in which we have made extended manometric studies More probably the barrier to urea is an energy-consuming metabolic process, and urea is actively "pumped out" of the brain as the plasma level falls

The mechanism requires further study, for it has obvious importance, theoretical and practical We are now engaged in experiments designed to test this barrier hypothesis

Summary

In 129 neurosurgical patients intravenous urea was used to reduce the intracranial pressure The main effect was a decrease in brain bulk, which made operation easier and safer Although arterial oozing was often increased in the early stages of operation, this was more of a nuisance than a danger The fall in intracranial pressure was measurable at lumbar puncture

No major toxic effects arose Local reactions were noted in the vein used, but they never progressed to thrombosis The blood-urea level rose and diuresis began shortly after the infusion was started, hence urea should not be given to patients with impaired renal function

Apart from its use during brain operations urea may serve (1) to tide over a comatose patient until he can be got to a neurosurgical centre, (2) for treating "the second-day slump", (3) for cases of acute head injury or tuberculous meningitis in which the intracranial pressure is high, and (4) for relieving benign intracranial hypertension

The most likely mechanism of the reduction of intracranial pressure is by means of a blood-brain barrier to urea

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DIAGNOSIS AND TREATMENT OF VASCULAR INSUFFICIENCY CAUSING PERCEPTIVE DEAFNESS

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GREAT advances have been made in the prophylaxis and treatment of conductive deafness Perceptive deafness, on the other hand, has been regarded as unamenable to any treatment The patient with perceptive deafness seldom hears well with a Medresco hearing-aid, and manufacturers have undertaken a great deal of research in an effort to help them

An analysis of all cases of deafness over a period of six years in this rural area of Northern Ireland reveals that perceptive deafness (including presbyacusis) is almost as common as conductive deafness The figures for conductive deafness have tended to decrease every year, but those for perceptive deafness have remained steady or increased slightly The efficacy of modern prophylaxis of conductive deafness, the increasing average age of the population, and the effects of acoustic trauma will inevitably raise the proportion with perceptive deafness

The objective of this study was to establish a means of alleviating symptoms and preserving function in perceptive deafness

Clinical Material

The investigation covered 981 cases of perceptive deafness seen in the six years 1953–58 Deafness was due to the following causes congenital deafness (50), virus deafness (27), traumatic labyrinthitis (6), acoustic and head trauma (31), and senile deafness (390)—504 cases in all The remaining 477 cases were of perceptive deafness without known cause Of these, investigation was considered to be inadequate in 160, leaving for consideration 317 (175 in males and 142 in females)

Findings

The following were apparently significant (1) age, (2) mode of onset, (3) presence or absence of vertigo, (4) presence or absence of fluctuation of the hearing level, (5) the effect of increase in blood-supply to the affected ear

Age —A purely arbitrary age of 40 years was taken and each case was placed in the under-40 or over-40 age-group Of the 317 patients, 106 were under 40 and 211 were over 40

Mode of onset —Two modes of onset were recognised—sudden (i e, deafness coming on in hours or days) and gradual The onset was sudden in 73 cases and gradual in 244 cases

Vertigo —135 patients had vertigo (observed or recorded in the history) and 182 had no vertigo

Fluctuation of hearing level —Each patient was specifically asked about such fluctuation, which was present in 122 cases and absent in 195 cases

Increase in blood-supply to affected ear —This was effected by blocking the sympathetic chain at or above the stellate ganglion In all cases an audiograph was done before and thirty minutes after the injection If hearing improved it did so in most cases within this period, but in a few cases improvement was delayed for several hours or more Any definite improvement in hearing, manifest within twenty-four hours of the injection, was attributed to the injection Hearing was thus improved in 85 cases and unimproved in 232 cases

TABLE I—DURATION OF DEAFNESS RELATED TO FLUCTUATION IN HEARING AND RESPONSE TO SYMPATHETIC BLOCK IN 271 PATIENTS WITH DEAFNESS OF KNOWN DURATION

Duration of deafness (yr)	Fluctuation		Response to sympathetic block	
	Present	Absent	Positive	Negative
Less than 1	52 (*51%*)	50	37 (36%)	65
1–5	32 (*47%*)	36	19 (28%)	49
Over 5	24 (*24%*)	77	19 (19%)	82

In fig 1 age is related to mode of onset, vertigo, fluctuation in hearing level, and effect of sympathetic block Sudden onset is slightly commoner in the younger age-group, and vertigo in the older, whereas fluctuation in hearing level and the effect of sympathetic block are unrelated to age

In table I duration of deafness is related to fluctuation in hearing level and response to sympathetic block The table shows that, the shorter the history, the more likely is fluctuation and the more likely is hearing to be improved by sympathetic block

In fig 2 sudden onset is related to vertigo, fluctuation of hearing level, and response to sympathetic block, in fig 3 vertigo is related to fluctuation in hearing level and response to sympathetic block, and in fig 4 fluctuation in hearing level is related to response to sympathetic block In table II sex is related to the other factors

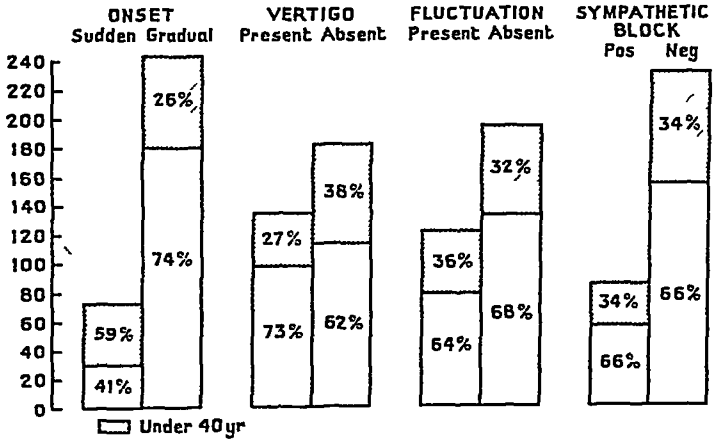

FIG 1—Patients ages related to mode of onset, vertigo, fluctuation in hearing level, and effect of sympathetic block in 317 cases of perceptive deafness

Clearly patients with fluctuation in hearing level are more likely to have vertigo, a positive response to sympathetic block is much commoner in patients with both vertigo and fluctuation (figs 3 and 4), and fluctuation in hearing level and improvement in hearing after sympathetic block are commoner in males than in females (table II)

It is apparent that early cases of fluctuating deafness with vertigo should respond best to measures designed to increase the labyrinthine circulation this is the "reversible group" (Wilmot 1957)

Ætiology

The factors producing perceptive deafness are usually described under two headings—

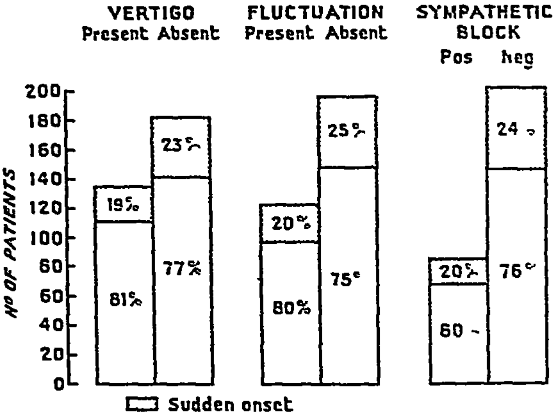

Fig 2.

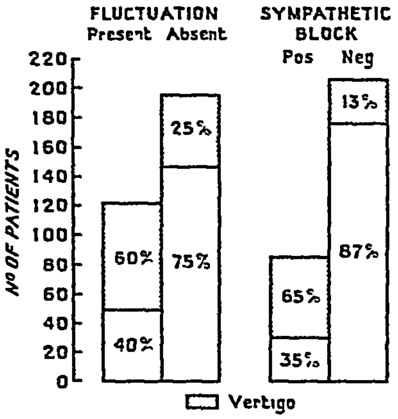

Fig 3

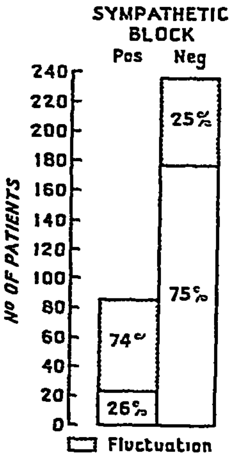

Fig 4

Fig 2—Mode of onset related to vertigo, fluctuation in hearing level, and effect of sympathetic block.

Fig 3—Vertigo related to fluctuation in hearing level and effect of sympathetic block.

Fig 4—Fluctuation in hearing level related to effect of sympathetic block.

congenital and acquired Of the congenital group, heredity and rhesus incompatibility are the most important In the acquired group maternal illness or malnutrition during pregnancy, neonatal illness or malnutrition, acute infections, especially in childhood (particularly mumps, influenza, and meningitis), acoustic trauma, head injury, hypertension, hypothyroidism, drugs Caisson disease, eighth-nerve tumours, and ageing have all been implicated

We believe, as does Simpson (1949), that in the vast majority of cases vascular insufficiency is an important

TABLE II—RELATION OF SEX TO OTHER FACTORS

Factor	Female (%)	Male (%)
Under 40 years	22	22
Sudden onset	33	33
Vertigo	41	43
Hearing improvement with sympathetic block	22	30
Fluctuation of hearing	22	38

underlying cause and that other factors have played no significant part Moreover we believe that in certain types of perceptive deafness (especially typical, Meniere's disease and sudden perceptive deafness in young people) the commonly associated psychological element of emotional tension and anxiety exists before the onset of symptoms, thus constituting another important ætiological factor In progressive deafness without fluctuation, this does not appear to apply to the same extent

Clinical Features

Deafness

In the common type of perceptive deafness, with or without vertigo, the onset of deafness is gradual Very often there is an intermittent loss of hearing, and thus the patient and his doctor may not realise its seriousness Such patients presenting themselves for the first time may be found to have normal, or almost normal, hearing in both ears, but on repeated examination their hearing will be found to fluctuate, they are usually well able to appreciate their own powers of hearing on any given occasion These fluctuations of hearing are often incorrectly assigned to nasal catarrh or eustachian obstruction One reason for this mistaken idea may be that periods of increased deafness are apparently linked with environmental cold and with upper-respiratory-tract infections, and many patients find that they are better in the summer than the winter One patient stated that he could regularly induce an attack of labyrinthine vertigo with increased deafness and tinnitus by drinking a glass of cold water

Initially, in patients with fluctuating hearing loss, long periods of normal hearing are interspersed with shorter periods of impaired hearing Later the periods of impaired hearing become longer and longer, and finally perceptive hearing loss is constant and severe Whereas in old age the common type of perceptive deafness is predominantly a *high-tone loss*, in the young or middle-aged adult seeking early advice the common type is a *low-tone loss*, when high-tone loss occurs in this group it is usually constant from the onset without any periods of improved or normal hearing

In other cases, usually in healthy young adults, the onset of deafness is alarmingly sudden Though usually unilateral, the deafness can come on simultaneously, or almost simultaneously, in both ears, and it is usually accompanied by vertigo, which may be severe In some cases a loud sound close to the ear seems to have precipitated the onset In this type of deafness the loss of hearing is usually profound and may be total and permanent Sometimes, however, there is gradual but incomplete recovery during the ensuing week or ten days, recovery rarely continues after this time (Wilmot 1959)

Sudden perceptive deafness associated with mumps and other systemic infections is also often complete and permanent, but is seldom accompanied by vertigo

Tinnitus

The type and tone of the tinnitus are very variable and have seemed of little help to us in investigating this disorder The intensity of the tinnitus usually accords closely that of the deafness Some patients are much more obsessed by their tinnitus, others by their hearing loss or vertigo When tinnitus is the only complaint, slight hearing loss on the affected side is usually found by pure-tone audiometry

Vertigo

The vertigo may, like the tinnitus, vary, but types and grades of vertigo can be distinguished more easily Vertigo has been defined as " an hallucination of movement of the patient in relation to his environment " (Cawthorne 1952), and this may be quite apparent to an intelligent patient, but others may have difficulty in analysing things so clearly and may confess merely to feeling “ dizzy ”, “ giddy ”, or “ light-headed ”

In a severe attack of labyrinthine vertigo the onset may be sudden or gradual Sometimes the onset is so sudden that the patient falls to the ground and may even injure himself in so doing Vomiting may be severe and prolonged, or the patient may have only nausea Spontaneous nystagmus may be observed Both deafness and tinnitus are often increased shortly before and during the period of vertigo The duration of the attack is very variable and is not necessarily related to its severity

Other Symptoms

These are common when looked for The majority of patients with an early inner-ear disorder have other head symptoms Genuine migraine may occur on the same side of the head, but is not so common as a feeling of fullness on the affected side this is often described as “ a stuffed-up feeling ” or “ a cotton-wool feeling ”—one patient with bilateral ear symptoms said he often felt as if he had a cap on his head when he had not

Hearing may be distorted, and this is characteristically an early symptom It is complained of most frequently by women and young people, who have greater opportunity to note it since they are often subjected to children’s voices and loud music

We have also seen cases with gustatory sweating on the same side of the face as the deafness and tinnitus

Cold hands and feet and chilblains with evidence of acrocyanosis are common in the younger female patients with inner-ear symptoms

Diagnosis

In the past there has been considerable bias towards diagnosing middle-ear deafness in any case where no obvious cause for deafness was present The first essential in the diagnosis of perceptive deafness is to exclude middle-ear deafness An accurate history, a simple clinical examination, and audiometry are usually all that is required, but where doubt persists other tests are necessary

In taking a history all the features of perceptive deafness should specifically be inquired into duration, variability, mode of onset and subsequent course of the deafness, and presence or absence of tinnitus, vertigo, or hearing distortion, the state of the general and peripheral circulation, other head symptoms, including migraine, relation to anxiety or grief, relation to external temperature, influence of nasal disorders, particularly head colds, vasomotor symptoms, the possibility of acoustic trauma, the family history, the previous history, the influence of surroundings—all may provide useful information and point towards conductive or perceptive deafness

In the doubtful case bone-conduction audiometry is useful, but insert masking must be used when the hearing loss is unilateral The pneumatic speculum and inflation of the eustachian tubes will help further Eustachian inflation should be done with the routine use of the nasopharyngoscope, and the hearing tested audiometrically before and after inflation Under these circumstances it is quite easy to show whether obstruction is, or is not, present and whether inflation has produced definite hearing improvement or not

True aural vertigo with perceptive deafness, associated with hypotension or normotension, characteristically gives an asymmetrical hearing pattern, whereas perceptive deafness associated with hypertension (and often also with vertigo) usually produces a symmetrical pattern in the hearing of the two ears

Except in the case of explosive damage to one ear, acoustic trauma also usually produces symmetrical hearing curves, and this is true, too, of occupational deafness (previous occupations may be of more significance than the present one)

Psychogenic deafness or malingering can usually be detected quickly by a skilled team Consecutive audiograms are dissimilar, and the audiometric findings do not fit in with the clinical picture

It is essential that in all cases of unilateral perceptive deafness the cranial nerves be tested, a recruitment test and caloric tests done, and X-ray examination of the internal auditory meati undertaken, if indicated, to exclude a neurofibroma of the eighth nerve

In bilateral and unilateral cases the blood-pressure should be recorded and the optic fundi and peripheral vessels examined for evidence of vascular disease

Smoking habits should be inquired into and recorded Heavy cigarette-smoking, although not perhaps of the same significance as in thromboangiitis obliterans, can adversely influence the progress of the disease

Incomplete congenital deafness may present difficulty in diagnosis, if the patient is first seen in adolescence or early adult life The initial interrogation of the patient or relative is therefore important

Premature senile deafness seldom comes on before the age of 50 and is usually accompanied by other stigmata of ageing The audiometric pattern, with symmetrical high tone-loss preponderating, is similar to that of presbyacusis coming on in old age

If the precise nature of the perceptive deafness is still obscure, special diagnostic procedures may help in differential diagnosis

Sympathetic Block

Just as eustachian catheterisation and the Rinne test are used routinely in the investigation of midde-ear deafness, we believe that the sympathetic fibres supplying the inner ear should be blocked as a routine test in certain cases of perceptive deafness If tinnitus and other subjective sensations are relieved and there is objective evidence of hearing improvement, this suggests that the induced vasodilatation has improved function and that the case is still in the reversible stage This improvement may be almost immediate or it may be delayed for several hours or days, and it is usually greatest when sympathetic release—evidenced by Horner’s syndrome and flushing of the tympanic membrane—is greatest It may last for a few hours only or persist indefinitely Improvement after sympathetic block does not occur in senile deafness, acoustic trauma, occupational deafness, or deafness associated with hypertension in fact, in this last disorder there is often a definite fall in the audiograph

Recruitment Test

The binaural or loudness balance test is a valuable confirmatory test of end-organ damage and should be done whenever possible, but it is not infallible It cannot be done when the difference between the hearing loss is maximal, or minimal, and is ideal when there is a 40–50 db difference between the ears at frequencies 1000–4000 c p s We have not found the monaural test of any value

Positional Tests

These tests can be carried out quickly as a routine procedure or more deliberately using electrical nystagmography Often a good history will give prior indication of the results of these tests Where there is considerable vertigo but little deafness, these tests are of value in revealing damage to the static labyrinth

Caloric Tests

All cases of perceptive deafness with vertigo should have these tests done. Water at 30 C and 44 C has been used, and the results recorded electrically, for the past two years These tracings form permanent records—a great advantage over the usual methods of recording, since they can be filed and compared with other tracings

Management

It seems likely that, in addition to a "constitutional factor" (i e , the patient's "make-up" conditioned by heredity, neonatal environment, emotional and physical experiences, smoking habits &c) there is a "precipitating factor" such as infection, cold, or sudden stress If this is correct, physical treatment, although very important, is only part of the management The otologist must have the closest possible cooperation of the family doctor and know as much as possible of his patient's background

In young normotensive patients the onset of the symptoms is often dramatically sudden, in such cases the response from the doctor responsible for treatment should be equally brisk, for delay in such cases may be disastrous so far as hearing is concerned

Patients presenting after many months or years of symptoms are often found to have permanent irreversible damage In this type of case treatment should be directed towards preserving the remaining function rather than trying to restore normal function—although exceptionally improvement may occur in spite of a long history

In older patients with genuine inner-ear symptoms the clinical picture is often obscured by hypertension These symptoms often resolve when the hypertension is under control

Obviously the patient with early symptoms—which must not be dismissed as functional—has the best prognosis The damage to the cochlea and vestibule is reversible initially in virtually all cases This reversibility may last for a very short time, possibly as little as four hours with severe vascular occlusion, or it may persist much longer, for years in some cases where vascular occlusion is intermittent and incomplete Success in treatment must depend therefore largely on the physician's ability to assess the degree of reversibility and his ability to do this *early* in each individual case Whereas it has long been recognised by many that anxiety symptoms are the rule in patients with typical Meniere's disease, it is not generally appreciated how often these symptoms have been present *before* the establishment of deafness, tinnitus, and vertigo We believe that the majority of inner-ear disorders of the "Meniere" type are "tension" phenomena, and that it is possible to predict from early symptoms that a patient will develop a fully fledged Meniere's syndrome if untreated

Treatment

Early cases with slight (10–20 db) low-tone unilateral deafness and tinnitus —Intelligent interest in the patient's symptoms, thorough investigation, firm reassurance simple sedation, and a promise of help should the need arise may be all that is required If deterioration occurs despite these measures, vasodilator therapy is indicated

Sudden onset of severe vertigo with tinnitus and unilateral deafness in a previously healthy normotensive patient —The acute attack should be treated by *immediate* stellate block followed by large doses of vasodilator drugs (e g , 30–40 mg or more of 'Perdilatal' daily, if necessary by the intramuscular route) Stellate block can be repeated as indicated by the patient's clinical and audiometric responses—it is more effective in the acute attack than vasodilators alone Once the severe vascular spasm has been relieved, oral vasodilator therapy (especially with perdilatal) often controls the condition Heavy sedation is not necessary if this treatment is applied efficiently

Similar treatment should be applied where sudden deafness develops with little or no coincident vertigo (Wilmot 1959) In both these classes of case, maintenance therapy with vasodilators may be indicated for the commonly associated acrocyanosis

Cases with 20–30 db or more loss of hearing and a history of from several weeks to a few months —Here a stellate block should be done as a diagnostic procedure under audiometric control It often causes a dramatic reduction in, or disappearance of, the tinnitus and head symptoms and sometimes improves the hearing Again, vasodilator therapy should follow and be continued for at least a month Symptoms are often reduced by prolonged vasodilator therapy alone

Cases in which the above measures have given some relief but have failed to check the progress of the condition —Repeated stellate block with intensive oral vasodilator therapy (up to 48 mg perdilatal daily) is occasionally successful in this type of case, but cervical sympathectomy is more economical of time and effort and more sure in its results Partial, occasionally complete, recovery of hearing and complete recovery of equilibration is common in this group

Sympathectomy is also indicated in the following conditions

1 When the patient has already a critical loss of hearing in one ear and the hearing in the good ear is progressively dropping

2 When the patient is deaf in one ear and has had an episode of temporary perceptive deafness in the good ear

3 When treatment has prevented further hearing loss on one or both sides, but failed to prevent continued incapacitating vertigo

4 Where there is a strong indication for sympathectomy on one side, we consider it best to operate on the other side also if there is any reasonable hope of restoring function or diminishing further loss of function This will usually depend largely on the age of the patient and the length of the history

Cases which have had persistent severe deafness and tinnitus for a relatively long period with incapacitating vertigo —Palliative therapy with sedatives, antihistaminics, or vasodilators may give some symptomatic relief in this group, and intelligent management may obviate the need for surgical destruction of the labyrinth, which we have done very rarely since our experience of other forms of treatment has grown

Other traditional measures —We have been unable to convince ourselves that any benefit whatever results from low-salt or low-fluid diets The use of barbiturates, tranquillisers, and antihistaminic drugs before investigation is complete may invalidate audiometric and, particularly, caloric responses Their use should therefore be reserved for treatment after an exact diagnosis has been made It seems likely that tranquillisers may prove to be more valuable than the barbiturates

Summary

A study of 317 cases of perceptive deafness, with and without vertigo, has shown that vascular insufficiency of the labyrinth is an important ætiological factor

In early cases this condition is often reversible if the appropriate treatment is applied In more advanced cases some prospect of improving function now exists

Vasodilators are of considerable value in certain types of perceptive deafness, but they should be used discriminatingly, and only after adequate investigation and when results can be checked by audiometry

This investigation would not have been possible without a generous grant to one of us (T J W) from the Northern Ireland Hospitals Authority We are also grateful to Mrs K Whelan, research technician in 1957–58, for her careful preparatory work, to Mr Duncan M Cheyne for the diagrams and statistical work, and to the directors of the Ferens Institute of Otolaryngology, Middlesex Hospital, for generous facilities

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URINARY ŒSTROGENS AFTER ENDOCRINE ABLATION

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DRAMATIC improvement in the clinical course of metastatic breast cancer in women may result from removal of the ovaries, adrenals, or pituitary gland The mechanism of this response is obscure and recent investigations suggest that it is not related to alterations in the excretion of those œstrogens which can be estimated chemically in the urine (Strong et al 1956, Bulbrook et al 1958a, b, and c) We now report a further study in which œstriol, œstrone, and œstradiol-17β have been estimated in the urine of patients with breast cancer before and after oophorectomy, adrenalectomy, and radioactive implantation of the pituitary (Forrest et al 1959)

Methods

The patients studied were women with inoperable or metastatic breast cancer treated by endocrine surgery Women of premenopausal years were treated in the first instance by removal of the ovaries only, adrenalectomy and pituitary implantation being reserved for those who failed to respond to this simpler measure or those in whom relapse followed initial benefit Postmenopausal women were treated initially either by adrenalectomy plus oophorectomy or by destruction of the pituitary with radioactive implants Response to these forms of therapy was judged on an objective basis, and improvement was accepted only when there was visible or radiological evidence of regression of tumour deposits

Urine was collected for œstrogen estimations while the patients were in hospital and taking a normal diet

Aperients known to give rise to abnormal pigments were not allowed The urine was collected in 3-day pools from which duplicate aliquots of 200 ml were used for analyses No steroid therapy was given during the preoperative or post-oophorectomy estimations, but after adrenalectomy and pituitary implantation the patients were given maintenance therapy of cortisone 50 mg per day In ten adrenalectomised patients the collections were made on the last 3 days of a 5-day period when 120 units corticotrophin gel was given daily These estimations have been differentiated in the figures by the letter C,

TABLE I—MAGNITUDE OF ERROR IN A RANDOM SERIES OF ŒSTROGEN ESTIMATIONS

Œstrogens	No of duplicate analyses	Mean excretion (µg per 24 hours)	Mean difference between duplicates (µg per 24 hours)
Œstriol	27	2 77±1 54*	0 26±0 25*
Œstrone	16	1 79±0 67*	0 22±0 23
Œstradiol-17β	12	1 55±0 90*	0 17±0 24

* Standard deviation

Although in most patients the estimations were carried out within 1 month of endocrine surgery, all those within 6 months have been included in the postoperative results provided that during this time the response of the patient and the maintenance therapy did not change Where several estimations were carried out on any one patient the mean value during the first 6 months after surgery has been used

The method of estimating œstriol, œstrone and œstradiol-17β was that of Brown (1955)

After acid hydrolysis of the urine the œstrogens were extracted by ether and fractionated by benzene-petroleum ether partition followed by methylation and chromatography of the methyl ethers on alumina Quantitative estimations of each fraction were made by the Kober colour reaction and the results calculated in microgrammes per 24 hours Any fraction containing an abnormal pigment was discarded In this laboratory recovery figures of over 80% of added œstrogens to acid hydrolysed female urine have been consistently obtained and the error between duplicate analyses has been within satisfactory limits (table I)

TABLE II—PREOPERATIVE EXCRETION OF ŒSTROGENS IN WOMEN TREATED BY ADRENALECTOMY PLUS OOPHORECTOMY AND BY RADIOACTIVE IMPLANTATION OF PITUITARY

Response of cancer		No	µg per 24 hours			
			Œstriol	Œstrone	Œstradiol	Total
Ax	Benefit	8	4 2±0 95	1 2±0 36	0 7±0 36	6 1±1 39
	No benefit	7	4 1±0 86	1 9±0 5	0 8±0 5	6 8±1·41
Hx	Benefit	9	4 2±0 56	1 8±0 49	0 48±0 25	6 4±1 12
	No benefit	16	5 0±0 69	1 5±0 31	0 33±0 23	6 9±0 80

Ax=adrenalectomy+oophorectomy Hx=pituitary implantation.

TABLE III—PREOPERATIVE EXCRETION OF ŒSTROGENS IN WOMEN TREATED BY ADRENALECTOMY AND OOPHORECTOMY

Response of cancer	No of patients	Mean excretion of œstriol, œstrone, œstradiol	
		µg per 24 hours	log µg per 24 hours
Benefit	8	6 1±1 39*	0 671±0 124
No benefit	7	6 8±1 41	0 734±0 130
Mean difference		0 7±1 99	0 063±0 181
P		>0 7	>0 7

* Standard error of mean

TABLE IV—PREOPERATIVE EXCRETION OF ŒSTROGENS IN WOMEN TREATED BY PITUITARY IMPLANTATION

Response of cancer	No of patients	Mean excretion of œstriol, œstrone, œstradiol	
		µg per 24 hours	log µg per 24 hours
Benefit	9	6 4±1 12	0 751±0·085
No benefit	16	6·9±0 80	0 772±0 069
Mean difference		0 5±1 48	0 021±0 122
P		>0 7	>0 8

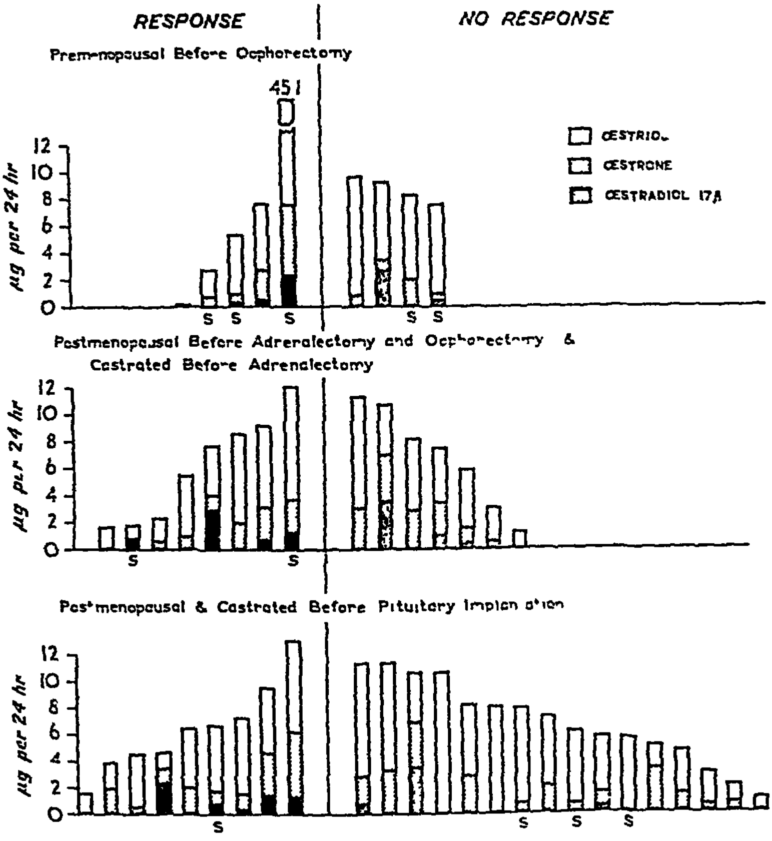

Fig 1—Preoperative levels of œstriol, œstrone, and œstradiol-17β in the urine of 39 patients with breast cancer treated by endocrine ablation

S=modified method of Brown et al (1957)

More recently the additional purification step introduced by Brown et al (1957) has been used in the estimations

This modification reduces interference by cortisone metabolites and may increase the recovery of œstrogens when maintenance therapy is being taken Analyses in which the modified method was used have been designated by the letter S in the figures For practical purposes we regard the lower limit of sensitivity of these methods as 1 µg of each œstrogen fraction per 24 hours

Results

Preoperative Estimations

The excretion of œstriol, œstrone, and œstradiol-17β was estimated in one or more 3-day pools of urine in thirty-nine women with breast cancer before endocrine surgery, several of whom were treated by more than one method of endocrine ablation In fig 1 the results have been arranged in three groups (1) estimations in premenopausal women before oophorectomy, (2) estimations in castrated and postmenopausal women before adrenalectomy or adrenalectomy plus oophorectomy, and (3) estimations in castrated and postmenopausal women before pituitary implantation It is clear that the response to endocrine surgery bears no relation to the preoperative levels of the three œstrogen fractions

The means of the arithmetic and logarithmic values of œstrogen excretion before adrenalectomy and before pituitary implantation in responding and non-responding patients are compared in tables II–IV The mean œstrogen levels in those patients whose cancer regressed did not differ significantly from those in whom no improvement occurred

Postoperative Estimations

The excretion of the three œstrogen fractions was also estimated in one or more 3-day pools in fifty women with breast cancer after endocrine surgery The results, which are arranged in an identical way to those before operation, again show no significant relation to the response to oophorectomy, adrenalectomy, or pituitary implantation (fig 2, tables V–VII) Comparison of the results after adrenalectomy plus oophorectomy and pituitary implantation indicates that significantly lower values follow the former operation (table VIII)

Preoperative and Postoperative Estimations

Estimations of urinary œstrogens were carried out in ten postmenopausal patients

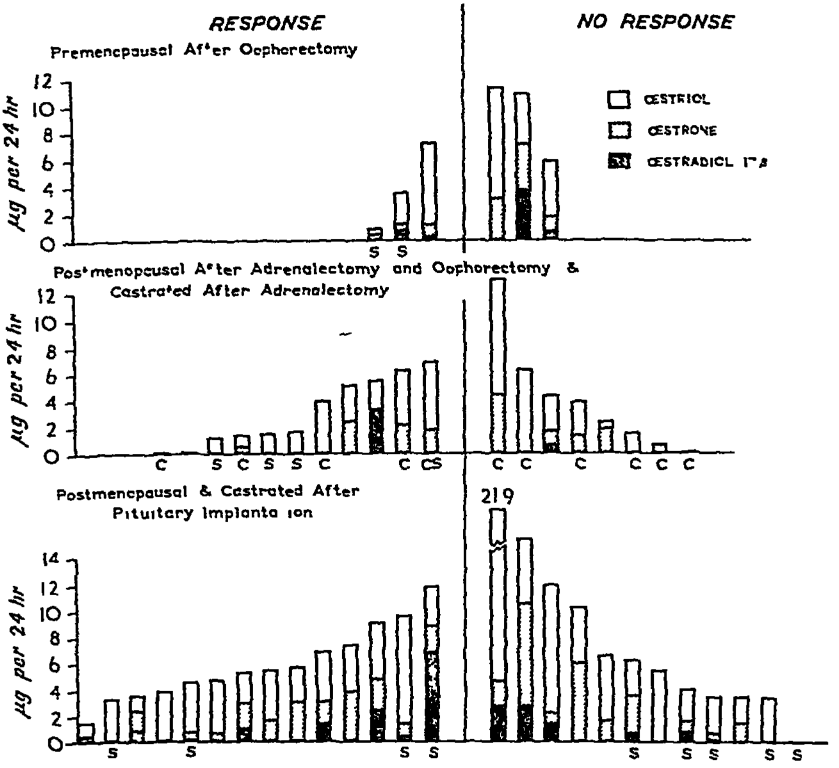

Fig 2—Postoperative levels of œstriol, œstrone, and œstradiol-17β in the urine of 50 patients with breast cancer treated by endocrine ablation

S=modified method. C=corticotrophin

before and after adrenalectomy plus oophorectomy and in fifteen postmenopausal patients before and after pituitary implantation (figs 3 and 4, tables IX–XII) The clinical response to these operations was not related to change in œstrogen levels Again it was noted that adrenalectomy plus oophorectomy was followed by a decisive drop in the excretion of the three œstrogens, whereas no consistent change resulted from pituitary implantation

TABLE V—POSTOPERATIVE EXCRETION OF ŒSTROGENS IN WOMEN TREATED BY ADRENALECTOMY PLUS OOPHORECTOMY AND BY PITUITARY IMPLANTATION

Response of cancer		No	µg per 24 hours			
			Œstriol	Œstrone	Œstradiol	Total
Ax	Benefit	11	1 9±0 56	0 8±0 97	0 3±0 29	3 0±0 71
	No benefit	8	2 7±1 13	1 2±0 51	0 1±0 06	4 0±1 48
Hx	Benefit	14	3 5±0 46	1 4±0 30	0 9±0 49	5 8±0 76
	No benefit	13	4 2±1 31	2 2±0 98	0 6±0 96	7·0±1 74

TABLE VI—POSTOPERATIVE EXCRETION OF ŒSTROGENS IN POSTMENOPAUSAL OR CASTRATED WOMEN TREATED BY ADRENALECTOMY

Response of cancer	No of patients	Mean excretion of œstriol, œstrone, œstradiol	
		µg per 24 hours	log µg per 24 hours
Benefit	11	3 0±0 71	0 375±0 104
No benefit	8	4 0±1 48	0 451±0 143
Mean difference		1 0±1 51	0 076±0 19
P		>0 5	>0 6

Discussion

Our results indicate that the preoperative levels of œstriol, œstrone, and œstradiol-17β in the urine of patients with metastatic breast cancer do not influence the response to oophorectomy, adrenalectomy, or pituitary implantation, and that these levels are of no value in predicting the results of endocrine surgery These findings, although differing from those of Huggins and Dao (1954) with a biological method of assay, are in agreement with those of Birke et al (1958) who also used Brown's method The specificity of this method is well established, the results correlating closely with œstrogen estimations carried out simultaneously by bioassay (Bulbrook et al 1957) counter-current distribution, reverse isotopic dilution (Gallagher et al 1958), and vaginal smears (Young et al 1957) Therefore there is little doubt that the lack of relation between the clinical response and the preoperative excretion of œstriol, œstrone, and œstradiol-17β is a reliable finding

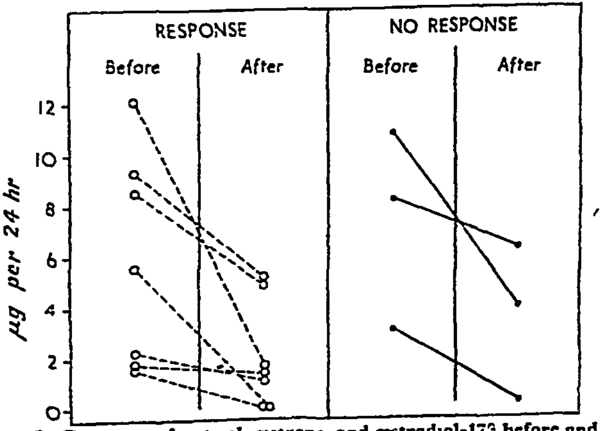

Fig 3—Excretion of œstriol œstrone, and œstradiol-17β before and after adrenalectomy in 10 postmenopausal patients with breast cancer

TABLE VII—POSTOPERATIVE EXCRETION OF ŒSTROGENS IN POSTMENOPAUSAL OR CASTRATED WOMEN TREATED BY PITUITARY IMPLANTATION

Response of cancer	No of patients	Mean excretion of œstriol, œstrone, œstradiol	
		µg per 24 hours	log µg per 24 hours
Benefit	14	5 8±0 76	0 711±0 06
No benefit	13	7 0±1 74	0·703±0 11
Mean difference		1 2±1 85	0 008±0 132
P		>0 5	>0 9

The postoperative estimations are generally less reliable because in many cases they approach the lower limits of sensitivity of the method and were made while the patients were receiving maintenance cortisone which is known to interfere with the results of Brown's original method (Brown et al 1957)

In studies reported elsewhere we have been unable to detect significant alteration in the postoperative excretion of œstrogens following stopping of maintenance therapy (Hobkirk et al 1959) and believe that on the whole the postoperative results reported in this paper do give a valid qualitative estimation of œstrogen excretion

Adrenalectomy plus oophorectomy regularly resulted in a fall of œstrogen excretion, but neither the extent of this fall nor the postoperative levels were related to the clinical response Several patients in both responding and non-responding groups continued to excrete significant amounts of the three œstrogen fractions, and in one patient, reported elsewhere, in whom œstrogen estimations were carried out monthly after adrenalectomy plus oophorectomy, levels of up to 10 µg were regularly found despite a most dramatic clinical remission (Sim et al 1959)

TABLE VIII—COMPARISON OF EXCRETION OF ŒSTRIOL, ŒSTRONE, AND ŒSTRADIOL-17β AFTER ADRENALECTOMY PLUS OOPHORECTOMY AND AFTER PITUITARY IMPLANTATION

Endocrine surgery	No of patients	Mean excretion of œstriol, œstrone, œstradiol 17β	
		µg per 24 hours	*log µg per 24 hours*
Adrenalectomy–oophorectomy	19	3 4±0 72	0 407±0·083
Pituitary implantation	27	6 4±0 92	0 707±0 062
Mean difference		3 0±1 25	0 300±0 102
P		<0 02	<0 01

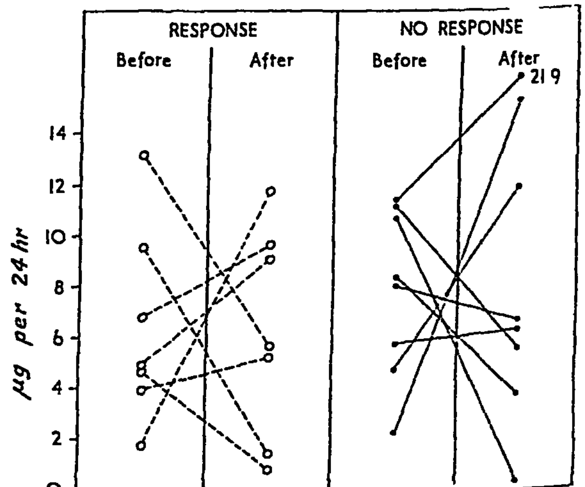

Fig 4—Excretion of œstriol, œstrone, and œstradiol-17β before and after pituitary implantation in 15 postmenopausal patients with breast cancer

TABLE IX—MEAN EXCRETION OF ŒSTRIOL, ŒSTRONE, AND ŒSTRADIOL-17β IN 10 PATIENTS BEFORE AND AFTER ADRENALECTOMY PLUS OOPHORECTOMY

Response of cancer	No of patients	Time of test	µg per 24 hours			
			Œstriol	Œstrone	Œstradiol-17β	Total
Benefit	7	Before	4 3	1 2	0 4	5 9
		After	0 9	0 7	0 5	2 1
No benefit	3	Before	3 8	2 3	1 2	7 3
		After	2 9	0 5	0	3 4

TABLE X—MEAN EXCRETION OF ŒSTRIOL, ŒSTRONE AND ŒSTRADIOL-17β IN 15 PATIENTS BEFORE AND AFTER PITUITARY IMPLANTATION

Response of cancer	No of patients	Time of test	µg per 24 hours			
			Œstriol	Œstrone	Œstradiol 17β	Total
Benefit	7	Before	4 0	1 8	0 5	6 3
		After	3 2	1 5	1 5	6 2
No benefit	8	Before	6 4	1 2	0 2	7 8
		After	5 3	2 5	1 0	8 8

TABLE XI—MEAN EXCRETION OF ŒSTROGENS IN 10 PATIENTS BEFORE AND AFTER ADRENALECTOMY PLUS OOPHORECTOMY

Time of test	Œstriol, œstrone, œstradiol (µg per 24 hours)
Before	6 3
After	2 5
Mean difference	3 9 ± 0 98*
P	<0 01

* Standard error of mean difference

TABLE XII—MEAN EXCRETION OF ŒSTROGENS IN 15 PATIENTS BEFORE AND AFTER PITUITARY IMPLANTATION

Time of test	Œstriol, œstrone, œstradiol (µg per 24 hours)
Before	7 1
After	7 6
Mean difference	−0 5 ± 1 92
P	>0 7

This finding is in agreement with those of other workers using Brown's method (Strong et al 1956, Bulbrook and Greenwood 1957, Bulbrook et al 1958b, Birke et al 1958) and bioassay (Bulbrook et al 1958d), although Diczfalusy et al (1958), using counter-current distribution, were unable to confirm that the Kober chromogens present in the urine of patients after adrenalectomy plus oophorectomy were in fact œstrogens Possible sources of œstrogens in the urine of patients after adrenalectomy plus oophorectomy have been discussed elsewhere (Hobkirk et al 1959)

We were unable to show that pituitary implantation had any consistent effect on œstrogen excretion Those patients who responded to the operation had values similar to those who failed to do so, indicating that the response was unconnected with the excretion of œstrogens This finding differs from that reported by Bulbrook et al (1958c) in which those patients who responded to surgical hypophysectomy had lower postoperative values than those patients who failed to benefit

The adrenal glands are not completely suppressed by removal of the pituitary Aldosterone secretion is unaffected by total hypophysectomy (McLean et al 1957) and we have also found that the secretion of androgens and cortisol may continue despite complete destruction of the gland (Forrest et al 1960) Under similar circumstances œstrogens also may be secreted by the adrenals and ovaries If this is so, it might suggest that removal of a pituitary factor may be responsible for the remission of breast cancer which may follow destruction of the hypophysis

Although these studies indicate that the response of breast cancer to endocrine ablation is not related to changes in the excretion of these three œstrogen metabolites in the urine, they do not refute the theory of œstrogen dependence It must be remembered that œstriol, œstrone, and œstradiol-17β represent only one-quarter of the total œstrogens excreted, and it may be that the active œstrogen is not yet isolated At the present time evidence for this is lacking, and there appears to be little justification for continuing the practice of referring to breast tumours which respond to endocrine ablation as œstrogen-dependent

We are indebted to Prof C F W Illingworth, in whose department of surgery these investigations were carried out, for his interest and criticism We also wish to thank Miss Shiela E Tilson, Mr Neil Carlin, and Mr Carrick Henderson for technical assistance This work was supported by the British Empire Cancer Campaign, A W Sim, R Hobkirk, Helen Stewart, and D W Blair being in receipt of full-time grants

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EFFECT OF A SATURATED MEDIUM-CHAIN TRIGLYCERIDE ON SERUM-LIPIDS IN MAN

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BECAUSE natural fats are complex their effects on serum-lipids during feeding experiments in man are very difficult to interpret The problem might well be clarified by studies using synthetic edible fats of simplified fatty-acid composition

Malmros (1958) suggested that the rise in serum-cholesterol level observed in man when butter or coconut oil is the sole source of fat may be due to the presence in before and after adrenalectomy plus oophorectomy and in fifteen postmenopausal patients before and after pituitary implantation (figs 3 and 4, tables IX–XII). The clinical response to these operations was not related to change in œstrogen levels. Again it was noted that adrenalectomy plus oophorectomy was followed by a decisive drop in the excretion of the three œstrogens, whereas no consistent change resulted from pituitary implantation.

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TABLE V—POSTOPERATIVE EXCRETION OF ŒSTROGENS IN WOMEN TREATED BY ADRENALECTOMY PLUS OOPHORECTOMY AND BY PITUITARY IMPLANTATION

Response of cancer		No	µg per 24 hours			
			Œstriol	Œstrone	Œstradiol	Total
Ax	Benefit	11	1.9±0.56	0.8±0.97	0.3±0.29	3.0±0.71
	No benefit	8	2.7±1.13	1.2±0.51	0.1±0.06	4.0±1.48
Hx	Benefit	14	3.5±0.46	1.4±0.30	0.9±0.49	5.8±0.76
	No benefit	13	4.2±1.31	2.2±0.98	0.6±0.96	7.0±1.74

TABLE VI—POSTOPERATIVE EXCRETION OF ŒSTROGENS IN POST-MENOPAUSAL OR CASTRATED WOMEN TREATED BY ADRENALECTOMY

Response of cancer	No of patients	Mean excretion of œstriol, œstrone, œstradiol	
		µg per 24 hours	log µg per 24 hours
Benefit	11	3.0±0.71	0.375±0.104
No benefit	8	4.0±1.48	0.451±0.143
Mean difference		1.0±1.51	0.076±0.19
P		>0.5	>0.6

Discussion

Our results indicate that the preoperative levels of œstriol, œstrone, and œstradiol-17β in the urine of patients with metastatic breast cancer do not influence the response to oophorectomy, adrenalectomy, or pituitary implantation, and that these levels are of no value in predicting the results of endocrine surgery. These findings, although differing from those of Huggins and Dao (1954) with a biological method of assay, are in agreement with those of Birke et al (1958) who also used Brown's method. The specificity of this method is well established, the results correlating closely with œstrogen estimations carried out simultaneously by bioassay (Bulbrook et al 1957) counter-current distribution, reverse isotopic dilution (Gallagher et al 1958), and vaginal smears (Young et al 1957). Therefore there is little doubt that the lack of relation between the clinical response and the preoperative excretion of œstriol, œstrone, and œstradiol-17β is a reliable finding.

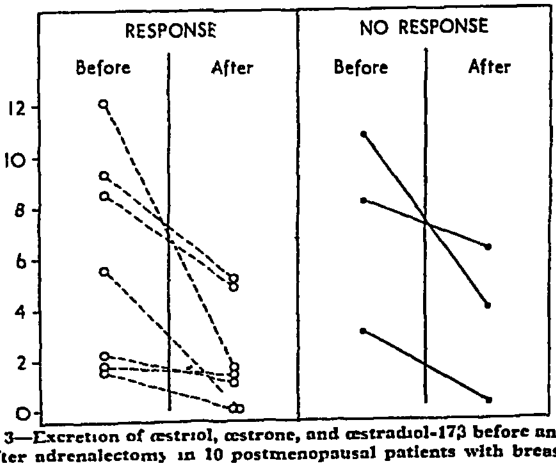

Fig 3—Excretion of œstriol, œstrone, and œstradiol-17β before and after adrenalectomy in 10 postmenopausal patients with breast cancer.

TABLE VII—POSTOPERATIVE EXCRETION OF ŒSTROGENS IN POSTMENOPAUSAL OR CASTRATED WOMEN TREATED BY PITUITARY IMPLANTATION

Response of cancer	No of patients	Mean excretion of œstriol, œstrone, œstradiol	
		µg per 24 hours	log µg per 24 hours
Benefit	14	5.8±0.76	0.711±0.06
No benefit	13	7.0±1.74	0.703±0.11
Mean difference		1.2±1.85	0.008±0.132
P		>0.5	>0.9

The postoperative estimations are generally less reliable because in many cases they approach the lower limits of sensitivity of the method and were made while the patients were receiving maintenance cortisone, which is known to interfere with the results of Brown's original method (Brown et al 1957).

In studies reported elsewhere we have been unable to detect significant alteration in the postoperative excretion of œstrogens following stopping of maintenance therapy (Hobkirk et al 1959) and believe that on the whole the postoperative results reported in this paper do give a valid qualitative estimation of œstrogen excretion.

Adrenalectomy plus oophorectomy regularly resulted in a fall of œstrogen excretion, but neither the extent of this fall nor the postoperative levels were related to the clinical response. Several patients in both responding and non-responding groups continued to excrete significant amounts of the three œstrogen fractions, and in one patient, reported elsewhere, in whom œstrogen estimations were carried out monthly after adrenalectomy plus oophorectomy, levels of up to 10 µg were regularly found despite a most dramatic clinical remission (Sim et al 1959).

TABLE VIII—COMPARISON OF EXCRETION OF ŒSTRIOL, ŒSTRONE, AND ŒSTRADIOL-17β AFTER ADRENALECTOMY PLUS OOPHORECTOMY AND AFTER PITUITARY IMPLANTATION

Endocrine surgery	No of patients	*Mean excretion of œstriol, œstrone, œstradiol-17β*	
		µg per 24 hours	log *µg* per 24 hours
Adrenalectomy + oophorectomy	19	3.4±0.72	0.407±0.083
Pituitary implantation	27	6.4±0.92	0.707±0.062
Mean difference		3.0±1.25	0.300±0.102
P		<0.02	<0.01

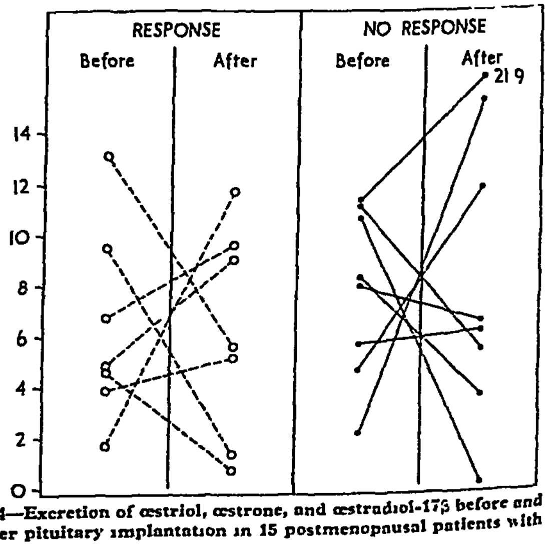

Fig 4—Excretion of œstriol, œstrone, and œstradiol-17β before and after pituitary implantation in 15 postmenopausal patients with breast cancer.

TABLE IX—MEAN EXCRETION OF ŒSTRIOL, ŒSTRONE AND ŒSTRADIOL-17β IN 10 PATIENTS BEFORE AND AFTER ADRENALECTOMY PLUS OOPHORECTOMY

Response of cancer	No. of patients	Time of test	µg per 24 hours			
			Œstriol	Œstrone	Œstradiol-17β	Total
Benefit	7	Before	4·3	1·2	0·4	5·9
		After	0·9	0·7	0·5	2·1
No benefit	3	Before	3·8	2·3	1·2	7·3
		After	2·9	0·5	0	3·4

TABLE X—MEAN EXCRETION OF ŒSTRIOL, ŒSTRONE AND ŒSTRADIOL-17β IN 15 PATIENTS BEFORE AND AFTER PITUITARY IMPLANTATION

Response of cancer	No. of patients	Time of test	µg per 24 hours			
			Œstriol	Œstrone	Œstradiol-17β	Total
Benefit	7	Before	4·0	1·8	0·5	6·3
		After	3·2	1·5	1·5	6·2
No benefit	8	Before	6·4	1·2	0·2	7·8
		After	5·3	2·5	1·0	8·8

TABLE XI—MEAN EXCRETION OF ŒSTROGENS IN 10 PATIENTS BEFORE AND AFTER ADRENALECTOMY PLUS OOPHORECTOMY

Time of test	Œstriol, œstrone, œstradiol (µg per 24 hours)
Before	6·3
After	2·5
Mean difference	3·9±0·95*
P	<0·01

* Standard error of mean difference.

TABLE XII—MEAN EXCRETION OF ŒSTROGENS IN 15 PATIENTS BEFORE AND AFTER PITUITARY IMPLANTATION

Time of test	Œstriol, œstrone, œstradiol (µg per 24 hours)
Before	7·1
After	7·6
Mean difference	−0·5±1·92
P	>0·7

This finding is in agreement with those of other workers using Brown's method (Strong et al. 1956, Bulbrook and Greenwood 1957, Bulbrook et al. 1958b, Birke et al. 1958) and bioassay (Bulbrook et al. 1958d), although Diczfalusy et al. (1958), using counter-current distribution, were unable to confirm that the Kober chromogens present in the urine of patients after adrenalectomy plus oophorectomy were in fact œstrogens. Possible sources of œstrogens in the urine of patients after adrenalectomy plus oophorectomy have been discussed elsewhere (Hobkirk et al. 1959).

We were unable to show that pituitary implantation had any consistent effect on œstrogen excretion. Those patients who responded to the operation had values similar to those who failed to do so, indicating that the response was unconnected with the excretion of œstrogens. This finding differs from that reported by Bulbrook et al. (1958c) in which those patients who responded to surgical hypophysectomy had lower postoperative values than those patients who failed to benefit.

The adrenal glands are not completely suppressed by removal of the pituitary. Aldosterone secretion is unaffected by total hypophysectomy (McLean et al. 1957) and we have also found that the secretion of androgens and cortisol may continue despite complete destruction of the gland (Forrest et al. 1960). Under similar circumstances œstrogens also may be secreted by the adrenals and ovaries. If this is so, it might suggest that removal of a pituitary factor may be responsible for the remission of breast cancer which may follow destruction of the hypophysis.

Although these studies indicate that the response of breast cancer to endocrine ablation is not related to changes in the excretion of these three œstrogen metabolites in the urine, they do not refute the theory of œstrogen dependence. It must be remembered that œstriol, œstrone, and œstradiol-17β represent only one-quarter of the total œstrogens excreted, and it may be that the active œstrogen is not yet isolated. At the present time evidence for this is lacking and there appears to be little justification for continuing the practice of referring to breast tumours which respond to endocrine ablation as œstrogen-dependent.

We are indebted to Prof. C. F. W. Illingworth, in whose department of surgery these investigations were carried out, for his interest and criticism. We also wish to thank Miss Sheila E. Tilson, Mr. Neil Carlin, and Mr. Carrick Henderson for technical assistance. This work was supported by the British Empire Cancer Campaign, A. W. Sim, R. Hobkirk, Helen Stewart, and D. W. Blair being in receipt of full-time grants.

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EFFECT OF A SATURATED MEDIUM-CHAIN TRIGLYCERIDE ON SERUM-LIPIDS IN MAN

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BECAUSE natural fats are complex their effects on serum-lipids during feeding experiments in man are very difficult to interpret. The problem might well be clarified by studies using synthetic edible fats of simplified fatty-acid composition.

Malmros (1958) suggested that the rise in serum-cholesterol level observed in man when butter or coconut oil is the sole source of fat may be due to the presence in

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TABLE I—FATTY-ACID COMPOSITION OF MCT BY GAS-LIQUID CHROMATOGRAPHY

A succinate polyester of ethylene glycol was used as the liquid phase, argon as the carrier gas, and strontium 90 was the detector

Fatty acid	% in MCT
C_6	1.9
C_8	77.7
C_{10}	19.6
C_{12}	0.8

these fats of saturated fatty acids of chain lengths less than C_{16}. Until recently it has been impossible to test this proposition adequately because of technical difficulties and the expense of glycerides containing only shorter-chain fatty acids.

In this study a synthetic fat, medium-chain triglyceride (MCT) was the sole source of dietary fat in formula-feeding experiments on human subjects. The serum-lipid responses obtained with MCT were then compared with those obtained when corn oil or butter was substituted in the formula diet in isocaloric amounts.

Material and Methods

The MCT preparation used in these experiments was extracted from coconut oil. The first fraction, collected by distillation of the fatty acids obtained by hydrolysis from coconut oil, comprises saturated fatty acids of 6–12 carbons. The fatty acids are then reconstituted into triglycerides (Kaunitz et al 1958). Thus, the C_6–C_{12} fatty acids constitute more than 99% of the fatty acids in MCT. The iodine value of MCT is less than 1. At the most only trace quantities of linoleic acid and non-saponifiable sterols are present in the preparation. The melting-point is below 0°C. MCT represents about 15% of the original coconut oil. At room temperature it is a very thin light-yellow clear odourless liquid, with a bland taste.

The fatty acid composition of MCT as determined by gas-liquid chromatography is shown in table I.

Studies were made in the metabolic ward of St Luke's Hospital on eight patients, one of whom served in two sets of experiments. A formula diet, prepared in a Manton-Gaulin Hospital on eight patients, one of whom served in two sets of dairy-type homogeniser, was the only source of food during the experiments (Ahrens et al 1954). The formula derived 40% of its caloric content from fat, 17% from protein, and 43% from carbohydrate. Dextrose was the only source of carbohydrate, and a purified casein preparation ('Casec') was the only source of protein. MCT, corn oil (iodine value 130), or butter (80% fat, iodine value 38) was used as a source of fat, each was substituted isocalorically during successive feeding periods without varying the protein or carbohydrate intake. We tried to keep the body-weight of each subject constant by adjustment of formula feeding. Sodium chloride, potassium chloride, and vitamins were given in constant amounts as daily supplements. All blood samples were drawn after an overnight fast. Serum was analysed two or three times per week for total and esterified cholesterol (Sperry and Brand 1943) and lipid phosphorus (Youngberg and Youngberg 1930). All the subjects were given each kind of fat for long enough to achieve a "steady state" with respect to the serum-lipids under measurement. Another fat was substituted isocalorically when three or more successive cholesterol determinations showed that a plateau had been reached. All of the formula diets were well tolerated except during a period of 3–4 days, characterised by nausea and abdominal fullness, before the subjects became adjusted to the MCT formula. But this transient discomfort did not prevent them from consuming and retaining the formula. Moderate constipation was a common complaint regardless of the fat source. No diarrhœa or change in the gross character of the stools was encountered.

TABLE II—SERUM-LIPIDS DURING SUCCESSIVE EXPERIMENTAL FEEDING PERIODS

Mean steady-state data are given, comparing effects of MCT and corn oil in four subjects on formula diets. (Individual peak values are included to indicate the transient early effects of MCT.)

Subject no	Age (yr)	Sex	Dietary fat	Mg per 100 ml serum (steady state)		
				Total cholesterol	Cholesterol ester	Phospholipids
1	42	M	Ad-libitum diet	227	169	218
			Corn oil	123	89	128
			MCT (transient peak)	180	132	150
			MCT	139	105	147
			Corn oil	117	89	145
2	46	F	Ad-libitum diet	232	169	247
			Corn oil	160	110	187
			MCT (transient peak)	190	140	202
			MCT	171	128	198
			Corn oil	158	105	185
3	54	M	Ad-libitum diet	212	164	244
			Corn oil	129	96	207
			MCT (transient peak)	165	121	213
			MCT	144	105	207
			Corn oil	136	100	208
4	52	F	Ad libitum diet	227	167	266
			Corn oil	152	106	205
			MCT (transient peak)	204	152	225
			MCT	150	107	210
Mean ± standard deviation			Ad-libitum diet	225 ± 8	167 ± 3	244 ± 20
			Corn oil	141 ± 17	100 ± 10	182 ± 36
			MCT (transient peak)	185 ± 16	136 ± 13	197 ± 32
			MCT	151 ± 11	111 ± 11	188 ± 32
			Corn oil	137 ± 20	98 ± 8	179 ± 32

TABLE III—SERUM-LIPIDS DURING SUCCESSIVE EXPERIMENTAL FEEDING PERIODS

Mean steady-state data only are included, comparing effects of MCT and butter in three subjects on formula diets. The effect of MCT following an ad-libitum diet is shown in two subjects.

Subject no	Age (yr)	Sex	Dietary fat	Mg per 100 ml serum (steady state)		
				Total cholesterol	Cholesterol ester	Phospholipids
5	62	F	Ad-libitum diet	269	194	275
			Butter	238	175	260
			MCT	177	126	190
			Butter	268	186	258
6	58	F	Ad libitum diet	259	184	265
			Butter	217	154	226
			MCT	179	131	217
4	52	F	MCT	150	107	210
			Butter	181	134	217
			MCT	131	94	198
7	62	F	Ad-libitum diet	357	258	288
			MCT	275	172	250
8	44	M	Ad libitum diet	188	140	232
			MCT	168	116	202

Results

Whenever a subject's regime was changed from an ad-libitum hospital diet to a formula diet, serum levels of total and esterified cholesterol, and of phospholipids fell regardless of the type of fat contained in the formula. The degree of fall varied with the nature of the fat in the initial formula (tables II and III). The four subjects who consumed a corn-oil formula after having an ad-libitum diet showed a mean drop in serum-total-cholesterol of 38 ± 6%[‡], the two who were given MCT had a mean drop of 23 and 11%, and the two who had butter showed a mean drop of 16 and 10%.

[‡] Standard deviation $\sqrt{\frac{\Sigma(\bar{x}-x)^2}{n-1}}$

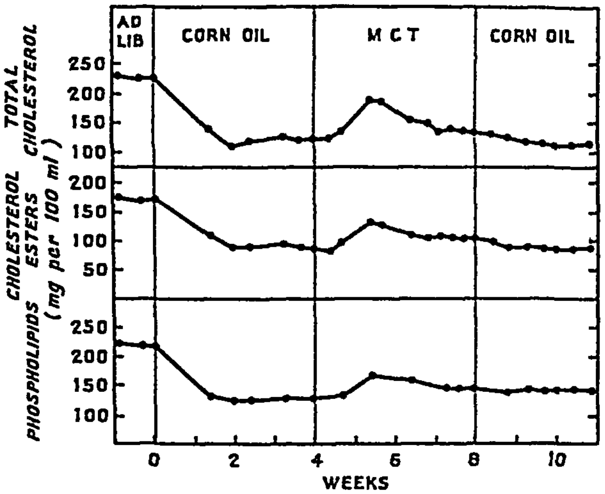

Fig 1—Effects on serum-lipids of a M C T formula diet compared with a formula containing an isocaloric amount of corn oil (subject 1, with a history of 'coronary insufficiency')

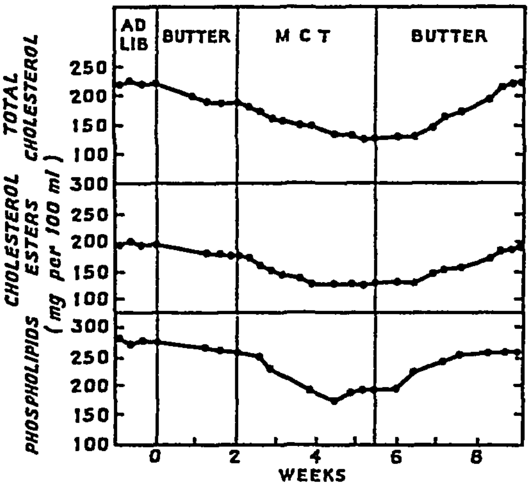

Fig 2—Effects on serum-lipids of a M C T formula diet compared with a formula containing an isocaloric amount of butter (subject 5, with a history of "coronary insufficiency")

In the four subjects in whom M C T was compared with corn oil, using each as his own control, the serum-lipids showed a prompt and dramatic drop when the diet was changed from an ad-libitum hospital regime to a corn-oil formula, as was previously reported (Ahrens et al 1957) When M C T was substituted isocalorically for corn oil, the serum-lipid values rose transiently in every case, with a mean maximal increment of 29±15% in 7–10 days (table II) Thereafter the serum-lipids fell gradually over a period of 10–22 days to levels slightly higher than those achieved with corn oil (fig 1) For example, serum-total-cholesterol levels (steady state) for the M C T periods averaged 8±5% higher than the serum-total-cholesterol levels (steady state) during the corn-oil periods, when M C T was given after corn oil When corn oil followed M C T, serum-total-cholesterol levels (steady state) fell by an average of 9±6%

In the subjects in whom M C T was compared with butter, the serum-lipid levels increased appreciably when butter followed M C T, and decreased appreciably when M C T followed butter (table III and fig 2) For example, butter induced rises in serum-total-cholesterol of 21 and 51% when it was given after M C T, but when M C T followed butter, decreases in the cholesterol level of 27, 26, and 16% were observed

Discussion

The cholesterol-raising effects of butter and coconut oil have been variously attributed to their low content of linoleic acid (Kinsell and Sinclair 1957), their low iodine value (Ahrens et al 1957), and their relatively high content of saturated medium-chain fatty acids (Malmros 1958)

Our studies show that the hypercholesteræmic effect of butter in relation to M C T cannot be due to its low content of linoleic acid or to its low iodine value, since M C T contains only a trace of linoleic acid and has an iodine value of less than 1 (butter having an iodine value of about 40) Nor is it likely that the hypercholesteræmic effect of butter is due to its content of medium-chain fatty acids, since M C T by itself has a hypocholesteræmic effect in relation to butter A possible explanation of the hypercholesteræmic effect of butter might still be that some combination of the fatty acids which it contains has an effect that cannot be predicted from the behaviour of individual fatty acids

A curious effect of M C T on serum-lipid levels was the transient rise which was produced after 7–10 days During subsequent weeks the lipid levels fell again to the values attained in the plateau-like phase of the earlier period This emphasises the difficulties of interpreting the results of formula-feeding experiments over periods of the order of 10 days or less

Ahrens et al (1957) have rated fats in terms of their effect on serum-total-cholesterol in relation to the effect of corn oil used as a standard According to this classification, M C T seems to fall into the same category as olive oil, and this observation is difficult to reconcile with the hypothesis of Ahrens et al that the hypercholesteræmic effect of a fat in relation to corn oil is best explained as a function of iodine value The results of our studies are more consistent with the suggestion that the effect of a dietary fat on serum-cholesterol can be related to certain of its physical characteristics By shortening the chain length of its constituent fatty acids, a fully saturated triglyceride acquires such properties as a low melting-point and greater miscibility with water—properties usually associated with a high degree of unsaturation (Deuel 1951)

Rittenberg et al (1937), Longenecker and Hilditch (1938), and Longenecker (1939) have shown that the saturated fatty acids with less than 12 carbon atoms, when ingested, are not significantly stored in animal depot fats More recently Geyer et al (1951) have shown that a shorter-chain fatty acid, such as octanoate, serves as an active substrate for oxidation but is not readily used for synthesis On the other hand a longer-chain fatty acid, such as palmitate, may serve equally well as a substrate for oxidation or synthesis depending on the metabolic circumstances But our studies do not show whether this dissimilarity in metabolism of fatty acids of differing chain lengths can account for the effect on serum-lipid levels of a highly saturated fat like M C T

Since corn oil is one of the most effective oils in lowering serum-cholesterol levels, it is noteworthy that M C T, a triglyceride with properties strikingly different from those of corn oil, raised the cholesterol levels in this small series in relation to corn oil by less than 10% Corn oil and M C T are at opposite ends of the lipid spectrum so far as iodine value, linoleic-acid content, and chain length are concerned The only characteristics they have in common are their liquid character at room temperature, relatively greater miscibility in water, and solubility in organic solvents

Summary

A medium-chain triglyceride preparation (M C T), containing saturated fatty acids with chain lengths ranging from C_6 to C_{12}, was incorporated into a formula-type diet and given as the sole source of fat to eight human subjects The effect on serum-lipids was compared with that of formula diets containing isocaloric amounts of corn oil and butter

Compared with corn oil, M C T induced a slight rise in serum-total-cholesterol when the experimental periods were long enough to permit a " steady state " In the subjects in whom M C T was compared with butter, the serum-lipids increased appreciably when butter followed M C T, and decreased appreciably when M C T followed butter

Thus the cholesterol-raising effect of butter cannot be due wholly to its content of medium-chain fatty acids, since M C T given alone lowers cholesterol levels in relation to butter The hypercholesteræmic effect of butter is difficult to explain in terms of iodine value, since the iodine value of M C T is much less than that of butter The cholesterol-lowering effect of M C T cannot be explained in terms of the content of linoleic acid or other polyunsaturated fatty acids, since they are not present in this preparation

Characteristics shared by M C T and the cholesterol-lowering oils, such as corn oil, are a low melting-point, relatively high miscibility in water, and increased solubility in organic solvents Possibly metabolic differences between M C T and triglycerides containing longer chain fatty acids might influence their effects on serum-lipids

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Addendum

Since this article was submitted, we have become aware of a study of the effect of dietary cholesterol on plasma-cholesterol levels (Beveridge, J H R , Connell, W F , Haust, H L , Mayer, G A *Canad J Biochem Physiol* 1959, 37, 575) in which a feeding experiment utilising M C T was described A formula-type diet providing 30% of its calories from M C T was fed for 8 days to a group of subjects previously on an isocaloric fat-free formula regime During this short experimental period the serum-total-cholesterol did not change significantly

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HUMAN FŒTAL THYROGLOBULIN
WITH PARTICULAR REFERENCE TO THE ÆTIOLOGY OF HASHIMOTO'S DISEASE

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ANTIBODIES to thyroglobulin have been found in the serum in various disorders of the thyroid gland, particularly Hashimoto's disease (Roitt and Doniach 1957) Experimental work by Witebsky (1957) suggests that this disease, at least, is caused by the action on the thyroid of antibodies produced by the patient's own tissues As antigens introduced into the body during fœtal development generally induce immunological tolerance instead of an antibody response (Billingham et al 1956) we thought it might be of interest to determine the age at which the fœtal thyroid gland begins to contain thyroglobulin

Investigation

Materials and Methods

Fœtal thyroid glands —Sixteen fresh fœtuses weighing 20 g to 3000 g were used The thyroid glands were dissected out, weighed, and homogenised in 1-2 ml of physiological saline solution In most cases a small fragment of the gland was examined histologically after fixation in formalin

Antiserum was produced in rabbits by immunisation with highly purified adult thyroglobulin, prepared as described previously (Korngold, van Leeuwen, and Brener 1959) It could detect the homologous antigen in quantities of less than 0 5 mg per ml Immunological analyses were done by the Ouchterlony technique as described by Korngold et al (1959)

Results

Since the immunological test used is not very sensitive, only the positive findings are significant The table shows that a substance antigenically indistinguishable from thyroglobulin was present in fœtuses the youngest of which was about 23 weeks old (no 11) The precipitation lines formed by the fœtal thyroid extracts fused completely with the line of the adult thyroglobulin, indicating that fœtal thyroglobulin is immunologically identical with the adult form

RELATION BETWEEN FŒTAL MATURITY AND PRESENCE OF THYROGLOBULIN

No of specimen	Weight of fœtus (g)	Crown-rump length of fœtus (cm)	Approx age in weeks (Potter 1952)	Weight of thyroid (mg)	Presence of thyro-globulin
1	3000		40	1090	+
2	3000		40		+
3	1600	28 0	32	750	+
4	1200	30 0	32		+
5	1110		30	250	+
6	920	25 0	28	400	+
7	880		26	450	+
8	780	22 0	26	270	+
9	770	21 0	26	210	+
10	460	18 8	23	200	+
11	420	20 0	23	150	+
12	278	12 5	18	100	−
13	127	13 8	18	50	−
14	115	12 0	16	35	−
15	39	9 5	14	30	−
16	20	7 2	12		−

Histological examination showed thyroid acini in all the glands examined (nos 1–4, 6, 7, 9, 11, 14) In most cases some of the vesicles contained colloid There was, however, no good correlation between the age of the

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Thyroid gland from a fœtus aged 23 weeks (no 11) There are acini in various stages of development some of which contain colloid (Hæmatoxylin and eosin × 200)

fœtus and the proportion of colloid-containing acini This is in agreement with the work of Lelkes (1933) The figure shows the histological appearance of the thyroid gland in the youngest fœtus in which thyroglobulin was found

Discussion

Radioactive iodine studies (Hodges et al 1955, Chapman et al 1949) have shown that the fœtal thyroid gland begins accumulating ^{131}I at the age of about 14 weeks This function is acquired simultaneously with the appearance of colloid in some of the acini Our investigation confirms that the human thyroid gland has begun to function by the 23rd week (4 months before birth) If our assay methods had been more sensitive we might have found that the appearance of thyroglobulin like the accumulation of ^{131}I, coincides with the development of colloid in the thyroid gland at about 14 weeks gestation (about 6 months before birth)

There are two mechanisms by which body components may become antigenic They may not yet be developed when tolerance to the body's own proteins is established, or they may normally have no opportunity to make contact with the body's mesenchymal cells (Burnet 1959) The critical age, after which tolerance is no longer present, varies in different species and even with different antigens (Billingham et al 1956) Nevertheless, man is not likely to be an exception to the rule that tolerance ceases at about the time of birth Our finding of thyroglobulin in fœtal thyroid glands 4 months before birth supports the view that thyroglobulin can act as an autoantigen, because normally the antigen is confined to the thyroid acini and does not reach the reticuloendothelial system

In Hashimoto's disease thyroglobulin has been observed outside the thyroid follicles (White 1957) This may be related to an abnormality of the basement membrane (Stuart and Allan 1958) Once thyroglobulin has escaped from the acini an immune response occurs which may cause further damage and thus perpetuate a vicious circle. The origin of the initial injury which allows leakage of thyroglobulin from the acini, is, however, still unknown

Summary

A substance antigenically indistinguishable from thyroglobulin was found in fœtal thyroid glands The youngest of these fœtuses was about 23 weeks old The gland showed colloid-containing acini

These results are keeping with the view that thyroglobulin is potentially autoantigenic because it is normally confined to the thyroid acini and does not come in contact with the body's antibody-forming mechanism

The bearing of these findings on the ætiology of Hashimoto's disease is discussed

We are grateful to Prof C Tupper and Prof R L de C H Saunders of the departments of obstetrics and anatomy, Dalhousie University, for permission to study the fœtuses

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Preliminary Communications

CHANGES IN RENAL AND URINARY ALKALINE PHOSPHATASE CONTENT FOLLOWING X-IRRADIATION OF THE RAT KIDNEY

X-IRRADIATION of the kidneys in the rat is followed by hypertension after a mean latent interval of 230 days[1] The blood-pressure was found to rise before the development of diffuse structural changes commonly described as "irradiation nephritis" or "sclerosis" It seemed possible that histochemical studies might reveal changes in enzyme content of the kidney in relation to the onset of hypertension Studies of alkaline phosphatase showed a marked reduction in this enzyme soon after irradiation, with a return to normal long before hypertension developed

INVESTIGATION

Twelve normotensive female rats of the Wistar strain, aged between 80–90 days and weighing 150–200 g, were exposed to 1200r irradiation of the kidneys by the technique of Wilson et al[1] They were killed serially at 1, 3, 5, 10, 20, and 40 days after irradiation The kidneys were immediately fixed in 80% ethyl alcohol, embedded in paraffin, and sectioned at 5 μ Alkaline phosphatase was demonstrated by the cobalt-sulphide technique of Gomori[2], sodium-β-glycerophosphate was used as substrate for an incubation period of 2 hours Three control animals received 1200r to the chest wall

Urinary alkaline phosphatase was studied in another series of twelve animals of similar age and weight Measurements were made for a baseline period of 7 days, thereafter six animals received 1200r irradiation to the kidneys while the remaining six served as controls Urinary phosphatase was estimated for 10 consecutive days after irradiation Measurements were made by the technique of Scott and Huggins,[3] the system being buffered at pH 9 2 A fivefold dilution of urine had to be used since it was found that with undiluted urine the ultimate colouration was too intense for estimation to fall within the most sensitive range of the photoelectric colorimeter, using a 6600 Å filter Serum alkaline phosphatase was also estimated on the 2nd and 6th day of the baseline period and the 3rd and 7th day of the post-irradiation period by the King and Armstrong[4] technique

Non-irradiated animals showed alkaline phosphatase in the brushborders, nuclear membranes, nucleoli, and

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[1] Wilson C., Ledingham, J M, Cohen M *Lancet*, 1958, i, 9
[2] Gomori G *Proc Soc exp Biol N Y* 1939 42, 23
[3] Scott, W W, Huggins, C *Endocrinology*, 1942 30, 107
[4] King, E J, Armstrong, A R *Canad med Ass J* 1934, 31, 376

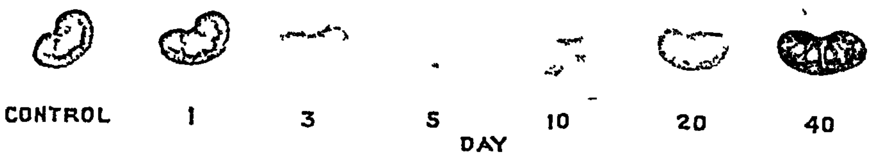

Fig 1—Alkaline phosphatase in rat kidney after 1200r band irradiation

mitochondria of the proximal convoluted tubule cells A day after irradiation mitochondrial positivity was lost but the other sites of enzymic activity were not affected until 3 days after irradiation A striking diminution in positivity of the brushborders occurred at this time and persisted until 40 days after irradiation, when full activity was restored and the kidneys were once more indistinguishable from those of non-irradiated control animals (fig 1) No change in renal alkaline phosphatase was demonstrated in the three animals which received irradiation to the chest wall

Urinary alkaline phosphatase content was inversely related to renal alkaline phosphatase positivity Maximal urinary concentration occurred between the 3rd and 8th day after irradiation (fig 2) There was no change in serum alkaline phosphatase concentration after irradiation Casts were absent from the urine and urinary pH was not altered by irradiation

COMMENT

Breedis et al [5] demonstrated that, when nephrosis was induced in rats with uranium nitrate, loss of renal alkaline phosphatase was associated with increased urinary excretion of the enzyme They found 15–46% of the total urinary phosphatase activity in the low-speed sediment in casts and other particulate matter, the remainder was thought to be incorporated in finely divided or soluble debris of the tubular cells Pasqualino and Bourne [6] observed loss of renal alkaline phosphatase up to the 8th day after renal artery clipping in rats Spink and Landeryou [7] noted loss of renal alkaline phosphatase in a variety of mammals, including man, as a result of endotoxin shock The varied nature of the insults which decrease renal alkaline phosphatase suggests that such loss represents a non-specific response to injury The observed increase in urinary excretion of the enzyme could not be related to the presence of casts, nor is it likely to be due to increased renal clearance, since serum levels showed no significant change following irradiation It appears therefore that " leakage " of alkaline phosphatase from the brushborders of the proximal convoluted tubule cells into the urine is the most likely explanation Estimation of renal and urinary alkaline phosphatase might therefore be useful as an index of tubular damage due to irradiation and other forms of renal injury So far, however, these studies have not shed further light on the mechanism of the hypertension which follows irradiation of the kidneys

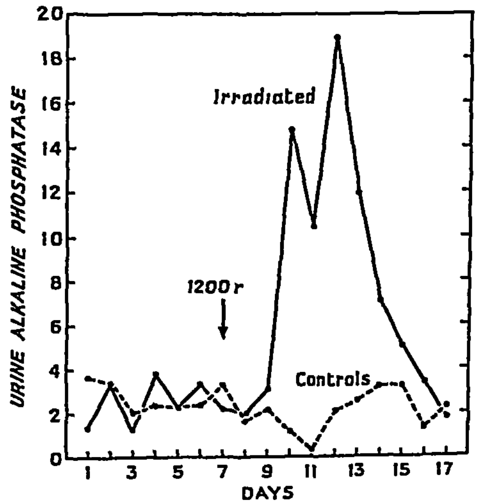

Fig 2—Changes in urinary alkaline phosphatase (King-Armstrong s per 100 ml) after irradiation of rat kidney (Six irradiated six controls)

We are grateful to Prof Clifford Wilson and Dr J M Ledingham for their advice

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5 Breedis, C , Flory, C M , Furth, J *Arch Path* 1943, 36, 402
6 Pasqualino, A , Bourne, G H *Nature, Lond* 1958, 182, 1426
7 Spink, W W , Landeryou, M J *J clin Invest* 1960, 39, 302

NEW ANTIVIRAL CHEMOTHERAPEUTIC AGENT ACTIVE AGAINST SMALLPOX INFECTION

ALTHOUGH smallpox vaccine has been used for over a hundred and sixty years the disease is still prevalent in many parts of the world, and in 1956 from those countries for which records are available 60,431 cases were reported with 31,622 deaths (52 2%),[1] and the actual number of cases must have been much higher In Burma, where vaccination is compulsory, there were 4223 notified cases with 1495 deaths (35 4%) There is therefore a definite need for a specific antiviral chemotherapeutic agent in the treatment of the disease

Isatin β-thiosemicarbazone has a pronounced chemotherapeutic effect in mice infected intracerebrally with neurovaccinia virus, and will protect against death after the injection of doses of virus up to 100,000 LD_{50} [2] It has no apparent effect in mice infected intracerebrally with ectromelia virus,[3] but it has a clear chemotherapeutic effect in mice infected with rabbitpox [4] A considerable number of derivatives of isatin β-thiosemicarbazone have been prepared and tested for antiviral activity,[5] and some have been found to be considerably more active than the parent compound In view of the activity of compounds of this type against two representatives of the pox virus group it was of interest to see whether they would also have an effect in infections with smallpox virus N-ethylisatin β-thiosemicarbazone, which was the derivative with the greatest activity against neurovaccinia virus, was chosen for this purpose

MATERIALS AND METHODS

The work was carried out with the Schofield strain of alastrim virus This was received as the seventh passage on the chorioallantoic membrane, and after one further passage on the membrane it was carried through three intracerebral passages in infant mice The virus produces a fatal infection in mice up to 6 days of age, in older mice signs of encephalitis

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1 Annual Epidemiological and Vital Statistics, 1956, pp 471–479 World Health Organisation, Geneva, 1959
2 Bauer, D J *Brit J exp Path* 1955, 36 105
3 Bock M *Z Hyg InfektKr* 1957, 143, 480
4 Bauer, D J , Sheffield, F W *Nature, Lond* 1959 184 1496
5 Bauer, D J , Sadler, P W *Brit J Pharmacol* 1960, 15 101

THERAPEUTIC EFFECT OF N-ETHYLISATIN β-THIOSEMICARBAZONE IN MICE INFECTED WITH ALASTRIM VIRUS

Expt no.	Treated				Controls		
	Dose level (mg. per kg.)	No. of mice	Died	Remained well	No. of mice	Died	Developed encephalitis and recovered
1	250·00	9	0	9	8	7	0
2	25·00	9	0	9	9	9	0
3	10·00	9	0	9	8	5	3
4	10·00	7	0	7	6	6	0
5	5·00	6	1	5	6	6	0
6	5·00	9	3	6	9	6	0
7	5·00	11	0	11	12	8	0
8	2·50	11	0	11		As expt 7	
9	2·50	8	1	7	8	3	5
10	1·25	11	1	10		As expt 7	
11	1·00	6	0	6	6	5	1
12	0·50	6	0	6		As expt 11	
13	0·50	8	1	7	8	5	3
14	0·25	8	3	5		As expt 13	
Totals		118	10	108	80	60	12

Dose conferring 50% protection 0·25 mg. per kg.

develop but many of the animals recover, and mice weighing 10 g. or more show no signs of illness.

The tests of chemotherapeutic activity were carried out in litters of mice of the same age and not more than 6 days old. The litters were pooled and redistributed to the mothers at random. The mice were then infected intracerebrally with a dose of virus containing about 10 mouse L.D.$_{50}$ or 10^1 pock-forming units. N-ethylisatin β-thiosemicarbazone was made up as a suspension in distilled water. The mice were weighed, and the dose selected for the experiment was injected subcutaneously with a micrometer syringe in a volume of 0·01–0·03 ml. The compound was injected at the time of infection or up to six hours later. In experiments with dose levels less than 25 mg. per kg. body-weight the dose was repeated once each day for five days.

RESULTS

The results of a number of separate experiments are shown in the accompanying table. After four to five days the control mice showed signs of cerebral irritation with occasional convulsions, followed by flaccid paralysis of one or more limbs, loss of weight, and death after five to ten days. In the first experiments high doses (25 and 250 mg. per kg.) of N-ethylisatin β-thiosemicarbazone were given in order to establish whether the compound had any antiviral effect. The treated mice showed no signs of illness at any time and were discarded in apparent health after four weeks. Further experiments were then carried out with dose levels down to 0·25 mg. per kg., also with positive results. Thus of 80 untreated mice 60 died and 12 developed encephalitis and recovered, whereas of 118 mice treated with N-ethylisatin β-thiosemicarbazone in dose levels ranging from 0·25 to 250 mg. per kg. 10 died and the remaining 108 survived without showing any signs of illness. The dose level which conferred 50% protection against infection was around 0·25 mg. per kg. The compound is of low toxicity; mice will tolerate a subcutaneous injection of 500 mg. per kg. given over a period of five days without showing signs of illness, and the therapeutic index is therefore greater than 2000.

CONCLUSIONS

The experiments thus demonstrate that N-ethylisatin β-thiosemicarbazone will protect mice against death and development of apparent illness after intracerebral infection with up to 10^2 L.D.$_{50}$ of alastrim virus, and that protection can be obtained with a dose level as low as 0·25 mg. per kg. An activity of this order is greater than that of the sulphonamides or the tetracyclines against bacteria, and gives reason to expect that N-ethylisatin β-thiosemicarbazone will be of clinical value in treating smallpox in man.

SUMMARY

Infant mice infected intracerebrally with 100 L.D.$_{50}$ of alastrim virus could be protected against death and the development of encephalitis by treatment with N-ethylisatin β-thiosemicarbazone at a dose level of 5 mg. per kg. The compound has a low toxicity and the therapeutic index is greater than 2000. The antiviral chemotherapeutic activity found in animal experiments is thus high enough to suggest that N-ethylisatin β-thiosemicarbazone may be of value in the specific treatment of smallpox in man.

We are grateful to Prof. A. W. Downie and Dr. K. R. Dumbell for providing the strain of alastrim virus and for much useful advice.

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Medical Societies

BRITISH ORTHOPÆDIC ASSOCIATION

THE spring meeting of the British Orthopædic Association was held in Glasgow, in conjunction with the Dutch Orthopædic Society and the Hand Clubs of Great Britain on April 7–9. The president, Mr. H. J. SEDDON, was in the chair. We publish below a summary of a few of the contributions.

Hand Surgery

Mr. I. A. MCGREGOR (Glasgow) described the different methods of skin grafting in the hand. He divided the grafts into free grafts and flaps. Free grafts could be whole thickness or split. Each had their advantages and disadvantages. The thinner the graft the more likely it was to take, but a thin graft tended to develop a contracture so that it often needed to be replaced later. In traumatic lesions early skin cover was essential to reduce fibrosis to a minimum. The graft must be applied to a suitable bed free from dead tissue and capable of capillary formation. Bone, cartilage or tendon were unsuitable. The free graft should overlap the defect and be fixed in position with sutures, the excess graft being removed at the first dressing. A bed unsuitable for a free graft was filled by a flap. A large defect might require an abdominal flap, intermediate defects a cross-forearm flap, and a smaller defect a cross-finger or thenar flap.

Mr. M. N. TEMPEST (Chepstow) said that the early differentiation between dead and living tissues in fresh soft-tissue injury was very important. Viability could be determined by the intravenous injection of either disulphine blue or kiton-fast green, which stained all living soft tissue whereas avascular tissues remained unchanged. Maximum staining was reached in 3–5 minutes and the dye was excreted by the kidney in about 48 hours. But Mr. G. BONNEY (London) wondered whether such early differentiation of avascular tissue would not result in tissue being excised which, given time, might have recovered, and Mr. Tempest agreed that this might apply to some tissues rendered temporarily avascular by tension.

Mr. C. C. JEFFERY (Exeter) said that open reduction and fixation of fractures of the hand was not often necessary but was of great value in certain cases: (1) displaced transverse and comminuted fractures in which closed methods had failed, (2) when external fixation would not maintain the position, (3) displaced or angulated fractures arriving late for treatment, (4) if vascular embarrassment rendered external splintage inadvisable, (5) when there was loss of bone. Kirschner wires provided a good form of internal fixation and a dental drill was useful in inserting them The wire should not traverse a joint which was intended to function again Certain oblique fractures including those into interphalangeal joints were fixed with transfixion pins Bone loss could be made good with cancellous bone from the ilium

Discussing motor and sensory recovery following repair of median and ulnar nerve lesions at the wrist, Mr Donal Brooks (London) said that motor recovery must take precedence over sensibility, so tendons and bones must be repaired first, though clearly the sooner nerves were repaired if they alone were damaged the better After repair of distal lesions of the ulnar nerve good motor recovery occurred in 4 out of 5, and of the median nerve in 2 out of 3 On the sensory side, 4 out of 5 repairs of both nerves gave useful recovery and 2 out of 3 reached the grade in which there was no over-reaction When one digital nerve was divided overlap from the other would take care of the anæsthetic area, but when both were divided they must be repaired He said that the right time to do nerve repair was when local conditions were most favourable, and there was no logical reason for primary repair Normal sensibility could never be restored after nerve repair, so the first consideration must be the recovery of protective sensibility If there was more recovery, so much the better, but the value of the recovery of sensibility depended on the use the patient made of it

Mr P S London (Birmingham) said that such great advances had been made in the reconstruction of the mutilated hand that it was too often assumed that these extensive procedures were always necessary It should be remembered that there were many failures, but these were not usually recorded He advocated a simple approach the minimum requirements of a useful hand were normal or near-normal sensitivity and two digits that could be brought together firmly and separated Tactile gnosis as defined by Moberg was not to be expected in any graft which had been separated from its normal nerve-supply, though many would attain protective sensitivity The initial operation was all important Often all that was necessary was wound toilet with preservation of as much normally sensitive skin as possible Small remnants of digits with normal skin should be preserved, but digits which had been denuded were usually better amputated The object of treatment should always be the earliest possible return to function of a hand unencumbered by stiff or insensitive fingers If this simple approach was followed many hands would be ready for use after only one operation, and within a few weeks, which had great psychological advantages

Prof J I P James (Edinburgh) said that most patients were first seen by casualty officers, however much we would like it to be otherwise Casualty officers should be taught the essentials of treatment wound excision, hæmostasis, skin cover, bandage with compression in a good position and elevation If this were done the hand would be in good condition for subsequent reconstruction if necessary Mr Muir disagreed he thought that patients with severe injuries of the hand should be transferred to special centres where expert treatment was available In modern times distance was no bar Immediate reconstruction was advisable and initial skin dressings should be given up

Mr Norman Capener (Exeter) supported the idea of simplicity in treatment, unnecessary details should be eliminated Good early treatment was essential, and the mutilated hand was as much of an acute emergency as anything in general surgery

Avascular Necrosis and the Head of the Femur

Mr James Patrick (Glasgow) said that the changes involved in avascular necrosis were different in cortical and cancellous bone, and in a fracture of the neck of the femur it was cancellous bone that was involved Firstly, there was a relative increase of density which was not always due to ischæmia, but even in the presence of ischæmia union would occur Secondly, there was a great increase in density due to mechanical collapse Normal fresh cancellous bone would not collapse if hammered, but if it had been kept at body-temperature for a year it would readily do so Thirdly, a pathological fracture occurred in the upper part of the femoral head Immediately after a subcapital fracture viability of the head was in doubt He advocated the use of a graft and a nail to improve the vascularity of the head and provide fixation The graft should never be introduced as far into the head as the nail because if the neck collapsed the graft, which would have united to the trochanter but not to the avascular head, would protrude into the joint If, when the nail was introduced, blood emerged from the central hole, the head was viable If blood could reach the bone cells in the femoral head within 15 days it would survive For this reason operation should be as early as possible If avascular necrosis needed treatment he advised in elderly people an Austin Moore prosthesis and in younger patients a trochanter-to-acetabulum arthrodesis The high incidence (70%) of avascular changes in children as compared with adults (50%), and in old age (10%), must indicate that blood-vessels cross the epiphysial line

Perthes' Disease

Dr J E Enklaar (Amsterdam) said that in the course of treating a child's hip in which Perthes' disease had been unresponsive to the usual conservative measures he had explored the joint In the course of the operation he had ruptured the ligamentum teres which did not bleed It was left in the joint Subsequent reconstitution of the femoral head had been surprisingly rapid Since then he had explored similar hips and had found the ligamentum teres to be shortened and unusually inelastic, so that when put on the stretch it produced deformity of the femoral head Examination of controls showed that the normal ligamentum teres contained thick-walled arteries and many arteriovenous shunts regardless of age There was a regular pattern of fine elastic fibres lying in parallel lines and a meshwork of autonomic nerve fibres The ligamentum teres removed from 10 patients with Perthes' disease showed consistently a second pattern of coarse fibres running at an angle to normal ones, and there was fragmentation of the autonomic nerve-fibres but no vascular abnormality He believed that changes in the autonomic nerve mechanism during growth resulted in the abnormal inelasticity of the ligament Unless this shortened ligament was either divided or relaxed in flexion (as he had done more recently) the changes in the capital epiphysis would persist

Congenital Dislocation of the Hip

Mr J A Wilkinson and Dr C O Carter (London) had investigated 200 children with congenital dislocation of the hip treated conservatively Results were seldom good in bilateral dislocations but could be successful when the condition was unilateral The outcome of treatment of unilateral dislocations could be foretold by an examination of the opposite hip If, after making allowance for age and sex, the roof of the opposite acetabulum was unduly oblique the result of treatment was likely to be unsatisfactory 149 patients were followed-up All but 8 had started treatment within the first 3 years of life and had been followed for 5–10 years There were 17 boys and 132 girls, 107 unilateral and 42 bilateral dislocations The results of bilateral dislocations were unsatisfactory and those unilateral dislocations in which the opposite acetabulum had a sloping roof were equally poor

A fairly accurate prognosis was thus possible at the child's first attendance The minority in whom the outlook was poor and those with bilateral dislocations might be better treated by surgery

Mr E W Somerville (Oxford) said that in those hips with only minor displacement it was wrong to say that the acetabular roof was shelving This was only the radiological appearance due to the delay of ossification, which was always seen in the presence of instability The acetabular roof was in fact normal in shape but cartilaginous Treatment by operation had been equally successful in unilateral and bilateral dislocations

Transplants of Bone

Dr M S Kingma (Amsterdam) said that Dutch orthopædic surgeons had gained great experience in the use of heterogenous bone by the use of refrigerated calf bone supplied by the bone transplantation service of the Netherlands Red Cross At first the results were encouraging Most wounds healed by first intention but sinuses developed in a few But later too many fractures showed persistent non-union He said that transplantation of calf bone would succeed only under the most favourable conditions The patient must be young, there must be good contact, firm fixation and prolonged immobilisation In fact calf bone was only useful in children for filling bone cavities Experience with homogenous bone showed that it was useful as a graft but less good than autogenous bone It was useful if autogenous bone was not available or in insufficient quantity It should not be used in spondylolisthesis in adults, for extra-articular arthrodesis, or for bridging defects

Mr JOHN CHALMERS (Edinburgh) said that there was a widespread belief that the more immature a tissue the more likely it was to survive when transplanted as a homograft He had carried out experiments with a strain of mice which by inbreeding had achieved such purity that homografts could be exchanged between individuals as readily as autografts These were called isografts Femurs from 18-day fœtal mice were implanted both as isografts and homografts into the spleens of adult mice At this age the femurs were mainly cartilaginous with a small ossific nucleus Each continued to grow equally up to the sixth day After that the cartilage of the isograft grew and was progressively replaced by bone, the secondary centres of ossification developing at the right time

In the homograft the cartilaginous part continued to grow but bone replacement ceased and the bone underwent necrosis These findings were strictly in accordance with the findings of transplanted adult homografts of bone and cartilage and showed that immature homografts had no advantage over mature homografts

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Reviews of Books

Osteochondritis Dissecans

I S SMILLIE, CH M, F R C S E, F R F P S, lecturer in charge, department of orthopædic surgery, University of St Andrews Edinburgh E & S Livingstone 1960 Pp 224 60s

Ambrose Paré was once called to see a master-tailor, living in the Rue Saint Honoré, who had a painful swollen knee He incised the joint, and out fell a loose body That was four centuries ago, and the first recorded instance of an arthrotomy yet it is interesting to reflect that very few operations have changed as little as this one, and, until very recently, any contemporary orthopædic surgeon would have managed the case in essentially the same way Unfortunately such treatment leaves a great deal to be desired when the fragment is derived from an articular surface, and there remains at its site of origin a gross irregularity which will provoke a secondary degenerative arthritis

In this monograph, Mr Smillie reviews four distinct conditions, occurring in different age-groups, which give rise to loose bodies, and have in common a radiological picture usually described as that of " osteochondritis dissecans " He goes on to show that if a loose body be replaced in its bed (after this has been freshened with a gouge or drill) it will heal back in position, and he has developed special instruments to facilitate this task of reposing and retaining the fragment

This is a valuable advance in the treatment of a disease which once carried a gloomy prognosis for the function of the joint Mr Smillie's methods have already been widely tried and acclaimed, and his colleagues will find this book an attractive guide to the minutiæ and rationale

A Textbook of Human Embryology

R G HARRISON, D M, Derby professor of anatomy, University of Liverpool Oxford Blackwell Scientific Publications 1959 Pp 244 45s

Professor Harrison's book includes the findings of recent investigations not yet mentioned in other textbooks of human embryology With many of these, especially in connection with endocrinology, spermatogenesis, and patterns of vascularisation in organs, the author himself has been concerned He has much reduced and simplified the later development of organs and systems, and in contrast he has emphasised what are sometimes called more "fundamental" matters Histogenesis of nervous tissue occupies no less than 9 pages (in a relatively small book), whereas development of the entire brain is covered in a mere 13 pages With this and similar changes of emphasis many readers will be in accord

A more succinct account of cardiac development is welcome, but the same brevity might usefully have been applied to the urogenital system Figures of the vascular tree of the testis are almost as numerous as those illustrating the entire development of the heart or brain These figures are excellent photographs of the author's preparations, contributing to the generally high standard of the volume's illustration

In treating brain development the author assumes that the reader will be familiar with the details of final form, which he rightly omits Nevertheless, much space is devoted to purely topographical description of the reproductive organs, and even the inguinal canal receives about $^1/_2$ page of text and 3 large illustrations (2% of the volume's 144 figures) These accounts do not depart from the information usually acquired in the dissecting-room

Despite what may seem to some readers to be occasional lack of proportion, Professor Harrison's text is a courageous departure Particularly to be applauded is his realisation that much minute detail can be jettisoned without loss of understanding Obviously he favours the growing conviction that attention to the basic processes of ontogeny greatly illuminates the particulars and makes them more interesting

Leucocyte Antigens and Antibodies

ROY L WALFORD, M D, assistant professor of pathology, University of California School of Medicine, Los Angeles New York and London Grune & Stratton 1960 Pp 182 $6 75

THIS monograph is the first in English on the subject Much work on leucocyte antigens has been published, as the bibliography of 567 references shows, but there is confusion and contradiction Dr Walford's critical survey is especially valuable in the important chapter on technique, in which he clearly indicates which methods he thinks will give the best and most consistent results Much of the book is devoted to a technical discussion of immunohæmatology It is clear that most leucoagglutinins are produced by blood-transfusion and are therefore isoantibodies Antibodies apart from transfusion-produced ones are rare and may be autoantibodies The recorded incidence of these leucocyte autoantibodies is reviewed, but the results are still far from clear and even the mechanism of drug-induced leucopenia has not been elucidated Dr Walford also discusses the relation of the L E-factor phenomenon to leucocyte antibodies, and the importance of leucocyte antibodies in the homograft reaction The chapter on clinical significance shows that the application of tests for leucocyte agglutination is at present limited, but they are becoming part of the investigation of leucopenic states Anyone beginning work on this subject will find this monograph a most valuable summary and a useful guide to what is known

Data for Biochemical Research

Editors R M C DAWSON, D C ELLIOT, W H ELLIOTT, K M JONES London Oxford University Press 1959 Pp 299 63s

THE laboratory worker is well used to handbooks such as the "Rubber Book" of the chemist, and he has received with gratitude the data brought together in the Merck and Geigy manuals This volume is a very welcome addition to the new species of abbreviated handbooks It brings together a great deal of information about compounds and reagents which biochemists use in their everyday research, and this has been achieved without producing an unwieldy tome More than half the book consists of a table of biochemical compounds, which is subdivided into nineteen alphabetically arranged sections. The first section deals with 182 aminoacids, peptides, and related nitrogenous compounds, the second with 151 carboxylic acids, alcohols, aldehydes, and ketones, the third with 127 phosphate esters, including nucleotides, the fourth with purines, pyrimidines, and nucleosides, the fifth with the spectral data and pK values for the compounds described in the fourth section, adding those of the nucleotides, the sixth with 77 carbohydrates and related compounds, and other sections deal with lipids and fatty acids, steroids, vitamins, porphyrins, chlorophylls, enzyme inhibitors, metal chelating agents, anti-metabolites, and so forth. Wherever appropriate, the following data are given for each compound: name, pseudonym, if any, structural formula, molecular weight, physical form, melting-point, optical activity, pK, solubility in water and organic solvents, references for preparation and estimation, and "general remarks".

The rest of the book tabulates enzymes used as laboratory agents, buffers, and physiological media, methods for the detection of biochemical compounds on paper, properties of ion-exchange resins, isotopes, manometric techniques, ammonium sulphate solutions, pH indicators, normal solutions, temperature, pressure conversions, and atomic weights. There is an extensive index which can be used as a guide to the different tables.

The editors, research-workers in Oxford and Cambridge, have skilfully welded the various contributions into a work which will undoubtedly become a standard volume in biochemical laboratories all over the world.

A Short History of Nursing

W. F. Bett, M.R.C.S., F.R.S.L. London: Faber & Faber. Pp. 125. 12s. 6d.

NURSING is, perhaps, the most practical of all aspects of medicine. Textbooks and theoretical instruction are relatively less important for the nurse in training than for the medical student. And it is significant that, when that indefatigable penwoman, Florence Nightingale, addressed herself to her colleagues, in her *Notes on Nursing*, even she rested content with less than 150 pages. It is also a very ancient calling and there is no doubt that such an authority as Dr. Bett could write, if he wished, a treatise on its history running to several volumes. But he has very wisely restricted himself to a slender book of the same dimensions as Miss Nightingale's, written with a flair and a brevity that will ensure its being read throughout the sorority. Apart from its main theme, his little book deals with the history of such things as the nurse's uniform, the instruments she commonly uses, and her diet. Even the most practical members of a practical profession will enjoy this brief excursion into its bibliography.

The Ætiology and Arrest of Pre-eclamptic Toxæmia with Early Ambulant Treatment

K. Douglas Salzmann, M.D., M.R.C.P.E., D.OBST., practitioner-in-charge, Dellwood General Practitioner Maternity Unit, Reading. London: H. K. Lewis. 1960. Pp. 69. 10s. 6d.

IN 1955 Dr. Salzmann[1] suggested that eclampsia was caused by maternal reaction to transplacental hormones from a fœtus or hydatidiform mole. He believed that there was first a reaction against these hormones and thus led to placental damage and the release of products which in turn caused toxæmia and eclampsia. The theory was little criticised at the time. In this volume the author is not so much concerned with ætiology as with the early detection and prevention of pre-eclamptic toxæmia. He is firmly convinced that the basic problem in toxæmia is vasospasm and that the first evidence of this is a slight elevation in diastolic blood-pressure. A rise of diastolic pressure above 84 mm. Hg is indicative of vasospasm and much of this short monograph is concerned with the place of reserpine in the management of these cases. He claims that the early use of reserpine by lowering the diastolic pressure and overcoming vasospasm prevents placental ischæmia and damage, and reduces the risk of toxæmia. From the trial he has conducted Dr. Salzmann argues that reserpine arrests the development of toxæmia in its earliest stages and in this respect is more efficient than bed rest. Emphasis is also placed upon the reduction of carbohydrate in the diet when the diastolic pressure is raised.

Dr. Salzmann produces many ingenious arguments in support of his theories but does little to help the reader sort out fact from fiction. Many statements are unsupported and it would be helpful to have the relevant references to the literature. Pygmies are said to have a high-protein/low-carbohydrate diet and not to suffer from toxæmia. Tall women with heavier babies are said to suffer more frequently from toxæmia and eclampsia, but this statement is not borne out by the studies of Nelson.[2] Dr. Salzmann repeats the commonly held view that eclampsia is more common in certain areas than others. While this may, indeed, be correct, Nelson is undoubtedly right when he claims that the truth of this statement remains to be tested.

In spite of these reservations, it is obvious that the author has thought a great deal about toxæmia, and obstetrician and physician will find much of interest in this book.

The Functions of the Endocrine Glands

Peter F. Hall, M.D., M.R.C.P., assistant physician, Sydney Hospital, and assistant lecturer in physiology, University of Sydney. Sydney: Horwitz. London: Pitman Medical Publishing Co. Philadelphia: W. B. Saunders. 1959. Pp. 290. 70s.

THIS book is written primarily for those interested in physiology, but with the increasing importance of physiology as a basis of clinical medicine, particularly in endocrinology, it should also be of considerable value to clinicians. It starts with a general account of the chemistry of hormones and their modes of action, which can easily be understood with the minimum of basic knowledge. Subsequent chapters deal with individual endocrine glands and related nervous mechanisms. Each chapter includes sections on embryology, anatomy, and histology (only those aspects strictly related to function) and on the biosynthesis of hormones, the control of their secretion, their actions, metabolism and fate in the body, tests of function, and the application of physiology in terms of disease.

The book is well written and readable and the layout is good, with clear headings and sufficient tabulation to enable the reader to extract the information he requires, without oversimplification. Subjects which are controversial or are not fully understood are discussed intelligently without introducing so many conflicting ideas as to confuse the reader. In the chapter on the adrenal cortex the physiological actions of the corticosteroids are not clearly differentiated from their pathological and pharmacological effects. The book is lavishly illustrated with chemical formulæ and diagrams, many of which are borrowed from works of leading authorities. There is a short but well-chosen bibliography at the end of each chapter.

British National Formulary, 1960 (London: British Medical Association and Pharmaceutical Press. 1960. Standard edition. Pp. 272. 7s. 6d. Interleaved copies 16s. 6d.).—Many new preparations have been added and some familiar but now seldom prescribed ones have had to be excluded. The lists of equivalent preparations and those with analogous therapeutic effect have been combined into one comprehensive glossary. The invaluable Notes for Prescribers at the beginning of the *Formulary* have been revised. A revised Alternative Edition, based on a pharmacological classification, will appear shortly.

The Merck Index of Chemicals and Drugs (7th ed. Rahway, N.J.: Merck & Co., Inc. 1960. Pp. 1641. $12).—The new edition of this valuable index contains nearly 10,000 descriptions of individual substances, more than 3300 structural formulæ, and about 30,000 names of chemicals and drugs alphabetically arranged and cross-indexed. There is now a separate and much expanded cross-index section of more than 30,000 names, which makes the pursuit of a substance much less arduous.

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[1] Salzmann, K. D. *Lancet*, 1955, ii, 953.

[2] Nelson, T. R. *J. Obstet. Gynæc. Brit. Emp.* 1955, 62, 48.

THE LANCET

LONDON 21 MAY 1960

Placenta Prævia

In Western Europe and the U.S.A. the number of maternal and fœtal deaths associated with placenta prævia fell dramatically in the first half of this century. Nowadays this condition rarely causes a maternal death, and the fœtal loss has dropped from 60 to 10%. Better maternal health, increased provision of antenatal beds, the development of an efficient blood-transfusion service, and the increased safety of cæsarean section have all contributed to the steady improvement.

In the management of this serious complication of pregnancy a big step forward was taken in 1945 when Johnson[1] and Macafee[2] showed that expectant treatment, by prolonging the pregnancy, greatly improved the outlook for the child without increasing the risk to the mother. Their claims have been confirmed by many in different parts of the world, and expectant treatment is widely practised. Nevertheless the correspondence that has followed Professor Macafee's article in our columns[3] shows that there are still unsettled issues in the management of placenta prævia. Most of the correspondence has been concerned with placentography. The accuracy of the technique has not been questioned, and this is not surprising for Reid,[4] Whitehead,[5] Hartley,[6] Lindsay,[7] and others have clearly demonstrated the precision with which a skilled radiologist can name the placental site. Opinions differ, however, as to whether placentography offers the clinician any real help in his management of the individual case. Macafee[3 8] believes that the case for placentography has been overstated, and his argument is strengthened by the knowledge that the excellent results he reports from his unit in Belfast are achieved without the help of radiology. He is supported by Stallworthy,[9] Theobald,[10] Browne,[11] Williams,[12] and Vartan.[13] On the other hand certain obstetricians, working closely with radiologists, are convinced that placentography has an important part to play in the management of placenta prævia. Percival and Murray[14 15] and Watson et al.[16] hold that, once placenta prævia has been excluded by radiography and bleeding has ceased, patients who have had a small non-toxic accidental hæmorrhage need not be kept in hospital. This represents a saving in antenatal beds and must be a considerable relief for those patients who are allowed home. Percival and Murray have not so far had cause to regret discharging these patients from hospital, but it would be of interest to learn the experience of other centres.

Percival[14] and Watson[16] and their colleagues have further established that placentography can reveal placenta prævia before bleeding has taken place. Both groups emphasise that the hazards of digital exploration of the lower uterine segment can be avoided altogether when radiography confirms the clinical impression that there is a major degree of placenta prævia. (Under these circumstances elective cæsarean section is carried out.) This point is very important, for any experienced obstetrician will acknowledge that, despite the greatest care, digital examination of the cervical canal and lower uterine segment may set off torrential hæmorrhage, and even today blood-transfusion is not without risks. Russell and Warrick[17] have shown how radiology can enhance the precision of surgical technique when a lower-segment section is performed for anterior placenta prævia. With the help of radiology the obstetrician is better able to avoid the bulk of the placenta and therefore, less likely to damage the fœtal circulation.

Other methods of locating the placental site have been tried from time to time. Techniques involving cystography, aortography, retrograde catheterisation of the femoral artery, radioactive isotopes, and amniography have been described, but none except amniography has found much favour in this country. Burke[18–20] has persistently advanced the case for amniography. One great disadvantage of this procedure is that the patient invariably goes into labour shortly after the contrast medium has been injected into the liquor.

Since the work of Stewart et al.[21] on leukæmia in childhood and its possible relation to antenatal X-ray examination, obstetricians have been more selective in their use of radiology, but it would be unfortunate if this caution were carried too far. The Adrian Committee[22] declared that there should be no hesitation in undertaking such investigations as placentography and pelvimetry when these are indicated. On balance placentography, correctly used, can probably contribute significantly to the management of cases of antepartum hæmorrhage, particularly when the placenta lies in the lower uterine segment.

The many manipulations previously applied at delivery were designed to save the mother's life, often at the expense of the fœtus. Valuable in their day, these procedures have now given way to cæsarean section, and most clinics report that 60–70% of their patients with placenta prævia are delivered abdominally. In modern obstetric practice lower-segment section is preferred, even when the placenta lies in the lower uterine segment, but this operation is not without risk

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1 Johnson, H. W. *Amer. J. Obstet. Gynec.* 1945, 50, 248.
2 Macafee, C. H. G. *J. Obstet. Gynæc. Brit. Emp.* 1945, 52, 313.
3 Macafee, C. H. G. *Lancet*, Feb. 27, 1960, p. 449.
4 Reid, F. *Brit. J. Radiol.* 1949, 22, 81.
5 Whitehead, A. S. *J. Fac. Radiol., Lond.* 1953, 4, 245.
6 Hartley, J. B. *Brit. J. Radiol.* 1954, 27, 365.
7 Lindsay, D. W., Davidson, J. K. *J. Obstet. Gynæc. Brit. Emp.* 1956, 63, 828.
8 Macafee, C. H. G. *Lancet*, April 2, 1960, p. 773.
9 Stallworthy, J. *Proc. R. Soc. Med.* 1959, 52, 565.
10 Theobald, G. W. *Lancet*, April 23, 1960, p. 921.
11 Browne, F. J. *ibid.* May 7, 1960, p. 1023.
12 Williams, L. *Proc. R. Soc. Med.* 1959, 52, 564.
13 Vartan, K. *ibid.* p. 565.
14 Percival, R., Murray, S. *Lancet*, 1955, i, 1045.
15 Percival, R., Murray, S. *ibid.* March 12, 1960, p. 596.
16 Watson, H. B., Israelski, M., Jordan, W. M. *Brit. med. J.* 1957, ii, 490.
17 Russell, J. K., Warrick, C. K. *Lancet*, 1955, i, 785.
18 Burke, F. J. *J. Obstet. Gynæc. Brit. Emp.* 1935, 42, 1096.
19 Burke, F. J. *ibid.* 1956, 63, 771.
20 Burke, F. J. *ibid.* 1957, 64, 596.
21 Stewart, A., Webb, J., Giles, D., Hewitt, D. *Lancet*, 1956, ii, 447. Stewart, A., Webb, J., Hewitt, D. *Brit. med. J.* 1958, i, 1495.
22 Radiological Hazards to Patients: interim report. H.M. Stationery Office, 1959. See *Lancet*, 1959, i, 975.

for the fœtus In opening up the lower segment the operator, if he encounters placenta, may damage the fœtal circulation and the baby may die from exsanguination **NELIGAN** and **RUSSELL**,[23, 24] who studied this hazard carefully for some years, showed that, in operating for placenta prævia, the obstetrician will find placental tissue anteriorly in 40% of cases With care the operator can usually avoid serious damage to fœtal vessels, but occasionally sufficient fœtal blood will be lost to threaten the life of the child Where placenta is encountered **NELIGAN** and **RUSSELL** look carefully for damage to fœtal vessels, and in certain cases carry out serial skin-prick hæmoglobin checks on the baby, if the hæmoglobin falls below 90% (13 3 g per 100 ml) a blood-transfusion is given The importance of their contribution is, first, that the operator can largely avoid the accident of fœtal blood-loss if he is aware of it, and, secondly, if there has been serious blood-loss the child's life can be saved by prompt transfusion

In England and Wales during the three years 1952–54 twenty-nine women with placenta prævia lost their lives,[25] and in most cases hæmorrhage was the sole cause of death The number of deaths is small, but it must be remembered that these were women in the prime of life—often with young families In the prevention of such deaths there is no substitute for clinical experience For example, the obstetrician, faced with hæmorrhage and difficulty in removing the placenta at cæsarean section, must recognise the occasional placenta accreta and know when to proceed without hesitation to hysterectomy **MACAFEE**[3] rightly draws attention to this difficult situation, in which delay may prejudice the mother's chances of survival In any event cæsarean section for placenta prævia should not be undertaken until cross-matched blood is available in the operating-theatre, and it is wise to set up an intravenous saline drip before anæsthesia is induced

Fœtal mortality associated with placenta prævia is still 10% in our leading maternity hospitals, and the figure for the whole country is probably higher This serious loss of fœtal lives remains a challenge to all branches concerned with maternity—including family practice, obstetrics, pædiatrics, radiology, and the blood-transfusion service

Immunisation Against Tetanus

ON a later page of this issue Dr G E **FULFORD** records that for England and Wales the Registrar General's returns show about 200 cases of tetanus a year, with a case-mortality of 27% The much improved case-mortality (it was 50% in the period 1931–41) and the relatively small number of cases must not be made an excuse for neglecting the effort needed to rid ourselves of this eminently preventable disease The true figures are likely to be higher than those in the official records, because some deaths will be certified as due to accident There is a disproportionately high incidence among children of school age, especially in rural areas The illness is a painful and distressing one, and each death an avoidable tragedy Moreover, there is a great deal of anxiety among thoughtfully anxious parents and young casualty officers about whether they have perhaps failed to identify a wound carrying a risk of tetanus Even the most careful parental and clinical care cannot eliminate anxiety of this kind The original injury is often trivial and may even escape notice

Passive immunisation, which involves injecting into the injured patient a dose of antitoxic serum from an actively immunised horse, confers immediate but rather brief protection lasting about two to three weeks, if the patient has previously had horse serum for any reason, protection may be very brief—a week or less—and the injection may induce severe anaphylaxis A great deal of passive immunisation against tetanus is carried out in this country **BOYD**[1] has cited **CONYBEARE**'s estimate that 750,000 doses are given each year, resulting in perhaps 50,000 cases of serum sickness with a few dangerous anaphylactic reactions

The surest way of preventing the anxieties, distresses, and deaths from tetanus, and the complications of passive immunisation, is to adopt a programme of active immunisation of children, combined with a method of recording the immunisation which will mean something to the casualty officer Active immunity is produced by subcutaneous infection of three 1 ml doses of tetanus toxoid, the second six to twelve weeks after the first Immunity is established a few days after the second injection, but a third injection is required six to eighteen months later Thereafter a dose of 1 ml every five years will keep the immunity at a sufficient level A patient so immunised needs no antitoxin if he is wounded, but he may be given a dose of toxoid Obviously this ideal will not be attained without some trouble, some very rare persons fail to produce antitoxin, and there are some particularly dangerous wounds, such as a penetrating injury to a man spreading dung on a field For these reasons, and perhaps for others, prophylactic antitoxin could probably not altogether be dispensed with even if active immunisation were generally accepted and fully recorded But certainly we could very nearly eliminate both tetanus and the complications of its serum prophylaxis by persuading all concerned to adopt active immunisation and useful recording But what is involved? In Putney, Dr **FULFORD** found that only about a fifth of the public had been actively immunised at some time This proportion will almost certainly fall when National Service ends, and the best hope lies in immunisation in early childhood and at school entry[2] Hospitals could help by offering active immunisation to all who have received a wound of any kind, those who required antitoxin should have their active immunisation later, as in the scheme lately described by **GARDNER**[3] Certainly such an effort would be worth making, but experience of public indifference to not very obvious dangers will prevent any great optimism about the

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[23] Neligan, G A Russell J K *J Obstet Gynaec Brit Emp* 1954, 61, 206

[24] Neligan G A Russell J K *Brit med J* 1955, i, 161

[25] Report on Confidential Enquiries into Maternal Deaths in England and Wales 1952 1954 H M Stationery Office 1957 See *Lancet*, 1957, ii 375

[1] Boyd, J S K *in* Symposium on Immunization in Childhood, p 81 Edinburgh 1960

[2] *ibid* see facing p 128

[3] Gardner, P A *Brit med J* April 23, 1960 p 1277

outcome. The only record of active immunisation that would provide sure information for the guidance of the casualty officer seems to be a tattoo mark. Record cards and disks would be satisfactory only if they were carried—and experience shows that this should not be expected. In short, we continue to have tragedies from tetanus because cases are too few to scare us into accepting the minor inconveniences of seeking active immunisation for ourselves and our children. It is easy to see why we are the despair of rationalists.

Lunar Journey

WE are so accustomed to artificial Earth satellites that an orbit no longer arouses a sense of wonder. Newspapers have lost interest in mere circumnavigation in space: this is a measure, not of public indifference, but of the speed of technological progress, and it seems certain we shall one day see a vehicle able to lift a man's weight to the moon and back.

Whether a man could survive the journey is another matter. Plans are well advanced in both Russia and the U.S.A. for the first step in human space travel. In Russia the latest step—an impressive one—has been the launching of a "spaceship satellite" weighing no less than $4^{1}/_{2}$ tons. In their "Project Mercury" the Americans expect to fire a man into orbit and bring him back after three circuits of the Earth. The physiological problems involved in such orbital flight are mainly the familiar ones of current practice in aviation medicine. The acceleration phase after launching is well within human tolerance, and, in a vehicle designed to reach orbital velocity, simple precautions such as correct posture and restraint are protection enough. The physiological measures necessary in the low barometric pressure at which military aviators fly are effective where there is no atmosphere at all, and any difficulty in providing a suitable environment is technological. The man in a space vehicle must have a cabin pressure sufficient to prevent decompression sickness, and he must wear a full pressure suit to protect him in case the cabin pressure should fall. So long as there is no fall in pressure his mobility and comfort are not greatly impeded since the suit need not be inflated; but his body surface must at all times be artificially ventilated, because pressure suits are made of fabrics through which water vapour cannot pass. Proper breathing mixtures must be supplied to his lungs whether his pressure suit is in use or not, and the temperature and humidity of the cabin atmosphere must be controlled within reasonable limits. He must have a chance of escape if things go wrong, at least from the time his vehicle is launched until it leaves the atmosphere and again when it returns to Earth. The technological difficulty of all this is simply that the space craft, unlike an aircraft, which maintains cabin pressure by compressing the atmospheric gases, must carry everything within itself—and this in a situation where weight is critical. Moreover a most exacting degree of internal temperature control is needed. As a satellite orbits from sunlight to shade, its surface temperature changes over a range of several hundred degrees; as it returns to the Earth's atmosphere it is heated to more than a thousand degrees by the sudden rise in friction.

About some aspects of orbital flight little is known. The phenomenon of weightlessness can be experienced for half a minute or so in certain aerobatic manœuvres. It is difficult to swallow dry food or to take liquids without inhaling them, and there is evidence that urinary urgency is diminished. But of the more dangerous effects which prolonged weightlessness may bring—severe disorientation perhaps, and hallucinations—not much is known. Many pilots flying alone at great altitudes are conscious of a sensation that all contact with the Earth has gone, that the aircraft has stopped in mid-air and will fall out of control if any manœuvre, however gentle, is attempted, and that the instruments have ceased to register the conditions of flight. This sensation can lead to panic. It arises, no doubt, from the absence of sensations normally associated with flight at lower altitudes, from the silence of the pressure cabin, the smoothness of the air, the lack of visual references outside the aircraft, and the remoteness from Earth. It has been called the "break-off phenomenon" and is probably related to the sensory deprivation states now receiving so much attention[1], and it may well affect and disable a susceptible space traveller. It remains to be seen whether any form of selection can eliminate the susceptible or any form of artificial stimulation replace the familiar sensations of terrestrial life.

Least of all is known about what may prove to be the greatest hazard of space flight. The Earth's atmosphere acts as an efficient shield against the primary cosmic radiation, which is not encountered below 75,000 ft. Above it a man will be exposed to immensely energetic particles which are capable of producing ionisation in human tissues. Some of them—the heavy primaries—seem able to cause actual focal damage towards the end of their path. At orbital altitudes the risks of ill effects may be small, especially if the orbit is in an equatorial plane, for the Earth's magnetic field, which is greatest at the equator, deflects the cosmic radiation.

The "Mercury" orbit height is likely to be between one hundred and two hundred miles, and the sortie to last about four and a half hours; the distance to the moon is a quarter of a million miles, and the journey there and back must take more than a day. The speed necessary for orbit is 18,000 miles an hour; to escape to the moon it is a third as great again. The provisions for a man's welfare on a lunar flight are bound to be more elaborate. The supply of gases, absorbants, and refrigerants for the pressure cabin, of food and drink for the pilot, of electric power for control and communications—all are considerably increased. Acceleration and deceleration values are greater either in magnitude or in duration. The mental strain of the longer flight through the silent, empty regions may test any man's fortitude, and there is an added radiation hazard, not only from the longer exposure, but from the Van Allen belts of high-intensity radiation which almost surround the Earth. Yet once

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[1] See *Lancet*, 1959, ii, 1072.

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About some aspects of orbital flight little is known The phenomenon of weightlessness can be experienced for half a minute or so in certain aerobatic manœuvres It is difficult to swallow dry food or to take liquids without inhaling them, and there is evidence that urinary urgency is diminished But of the more dangerous effects which prolonged weightlessness may bring—severe disorientation perhaps, and hallucinations—not much is known Many pilots flying alone at great altitudes are conscious of a sensation that all contact with the Earth has gone, that the aircraft has stopped in mid-air and will fall out of control if any manœuvre, however gentle, is attempted, and that the instruments have ceased to register the conditions of flight This sensation can lead to panic It arises, no doubt, from the absence of sensations normally associated with flight at lower altitudes, from the silence of the pressure cabin, the smoothness of the air, the lack of visual references outside the aircraft, and the remoteness from Earth It has been called the "break-off phenomenon" and is probably related to the sensory deprivation states now receiving so much attention[1], and it may well affect and disable a susceptible space traveller It remains to be seen whether any form of selection can eliminate the susceptible or any form of artificial stimulation replace the familiar sensations of terrestrial life

Least of all is known about what may prove to be the greatest hazard of space flight The Earth's atmosphere acts as an efficient shield against the primary cosmic radiation, which is not encountered below 75,000 ft Above it a man will be exposed to immensely energetic particles which are capable of producing ionisation in human tissues Some of them—the heavy primaries—seem able to cause actual focal damage towards the end of their path At orbital altitudes the risks of ill effects may be small, especially if the orbit is in an equatorial plane, for the Earth's magnetic field, which is greatest at the equator, deflects the cosmic radiation

The "Mercury" orbit height is likely to be between one hundred and two hundred miles, and the sortie to last about four and a half hours the distance to the moon is a quarter of a million miles and the journey there and back must take more than a day The speed necessary for orbit is 18,000 miles an hour to escape to the moon it is a third as great again The provisions for a man's welfare on a lunar flight are bound to be more elaborate The supply of gases, absorbants and refrigerants for the pressure cabin, of food and drink for the pilot, of electric power for control and communications—all are considerably increased Acceleration and deceleration values are greater either in magnitude or in duration The mental strain of the longer flight through the silent, empty regions may test any man's fortitude, and there is an added radiation hazard not only from the longer exposure, but from the Van Allen belts of high-intensity radiation which almost surround the Earth Yet once manned orbital flight has been achieved, these difficulties should not be insuperable and may be met by development of existing techniques. Biological systems for respiratory-gas exchange, food synthesis, and recycling of urine may prove necessary for space flights lasting months or years. The radiation hazard is more difficult to assess, but even the Van Allen belts appear incomplete and may be avoided by a polar escape route.

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[1] See *Lancet*, 1959, ii, 1072

For all its serene beauty, the moon seems to be a desolate place: deep wide valleys and high mountains exposed to the whole radiation spectrum, to micrometeorite bombardment, and to temperature changes from 212°F to −243°F, days and nights a fortnight long, an ambient pressure of 10^{-13} part of an atmosphere. The explorer may find some shelter in deep caves, but he will have to wear his pressure suit and carry with him an oxygen supply wherever he goes—not a great burden in the moon's low gravitational field. Even in this inhospitable climate there may be life of sorts, and it would be prudent to ensure that a returning spaceship brings back no unwelcome lunar guests in the shape of micro-organisms able to multiply on earth. Desolate though the lunar scene may be, and however long and hazardous the journey, there seems to be no fundamental physiological bar to success. The legends of the nursery are about to give way to the achievements of science.

Annotations

AGREEMENT ON HUMAN CHROMOSOMES

ONE summit conference which has reached a most welcome and complete measure of agreement is that which met last month in Denver to settle the nomenclature of human chromosomes. The system agreed upon was described in our last issue (p. 1063), and there seems every prospect that it will be accepted as a standard system.

It is only recently that we have been able even to count human chromosomes, and the identification of individual pairs is still a matter of considerable difficulty. The earliest anomalies to be described concerned only the X and Y chromosomes and the second smallest autosome pair (the "mongol" chromosome, now no. 21), and very little difficulty arose over the nomenclature of these. But as other rarer defects come to be described,[1–4] involving other chromosomes and possibly more than one at a time, precision becomes essential: all the more so when there exists the possibility of disagreement over the interpretation of some cases.

Independent groups of workers have evolved, as their studies progressed, various systems of nomenclature. Most have been based on a numerical system, arranging the chromosomes in order of length. The system with which most people in this country are familiar, that of Ford, Jacobs, and Lajtha,[5] is in one respect an extreme example of this, for it includes the X chromosomes in the series. Alternatively, one may emphasise the grouping of chromosomes, as is done in the system used by the French workers who first described the extra chromosome of mongolism.[6] The latter is in some ways the more natural system: in practice, one begins analysing a mitosis by first separating the groups, the biggest (1–5), the "wish-bones" (the blessedly characteristic groups of three pairs, 13–15, near the middle range of size with the centromere very near the end), and the smallest acrocentrics (21, 22, and Y) coming out relatively easily. Ford et al.'s system was affected by the grouping tendency, the chromosome pair now called 16 appears on their list in an anomalous position because they wished to group it with the much smaller pairs 19 and 20 on a basis of arm ratio. In the event, it has been decided to adopt the criterion of length almost exclusively, the autosomes being numbered from 1 to 22 entirely on this basis (save for some irregularity in the wish-bones 13–15, possibly dictated by the order of prominence of satellites), but leaving out the sex chromosomes, labelled separately as X and Y. The new system corresponds exactly to none of its predecessors, though it is nearest to that of the Uppsala group.

It is almost certainly the best system that could be devised at present. The group which worked it out consisted of representatives of all the teams of workers who had up to March of this year published detailed analyses of human mitoses. Seventeen members (eight American, four British, three Swedish, one French, and one Japanese) were invited to Denver by the University of Colorado. It is very encouraging to find that so diverse a group were able to reach agreement so quickly. It is to be hoped that other workers entering the field will endeavour to adhere to the new convention. So far as possible, we hope our contributors will use it, or, if they prefer, supply a key to their own system in terms of the new standard.

The new system lacks a good label: it cannot be identified by any one author's name. May we suggest that, in gratitude to the hosts of last month's meeting, it should be called the Denver system, and that chromosomes identified on this system be called, for instance, pair no. 16 (Denver)?

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[1] Polani, P. E., Briggs, J. H., Ford, C. E., Clarke, C. M., Berg, J. M. Lancet, April 2, 1960, p. 721.
[2] Fraccaro, M., Kaijser, K., Lindsten, J. ibid. p. 724.
[3] Edwards, J. H., Harnden, D. G., Cameron, A. H., Crosse, M., Wolff, O. H. ibid. April 9, 1960, p. 787.
[4] Patau, K., Smith, D. W., Therman, E., Inhorn, S. L., Wagner, H. P. ibid. p. 790.
[5] Ford, C. E., Jacobs, P. A., Lajtha, A. Nature, Lond. 181, 1565.
[6] Lejeune, J., Turpin, R., Gautier, M. Ann. Genet. 1959, 2, 41.

TUMOURS OF SALIVARY GLANDS

THE results of the treatment in Saskatchewan Province of 129 cases of tumour of the salivary glands have been reviewed by Prof. E. M. Nanson in a Hunterian lecture.[1] The standard treatment was local removal followed by irradiation. 79 tumours were classified as "benign mixed tumours"—62 primary and 17 recurrent. 2 of the primary and 3 of the recurrent tumours had returned at the time of review. Professor Nanson compares these results with those in other recorded series in which the recurrence-rates were up to 40%, and he attributes the improved results in his series to routine irradiation. But what he cites as the recurrence-rates of some workers is the percentage of all cases with recurrence, including those with recurrence at the time of treatment—a percentage similar to that in his own series.

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[1] Nanson, E. M. Ann. R. Coll. Surg. Engl. 1960, 26, 157.

Of another 17 cases classified as "malignant mixed tumours", 6 had recurred It would have been interesting to know whether in any, and if so in how many of these cases the diagnosis had been revised from an original one of benign mixed tumour as a result of the clinical behaviour of the tumour If there were any such revisions the recurrent cases might legitimately have been added to those of the benign mixed tumour group In the other types of malignant parotid tumours the five-year mortality-rate was 20–60%

Professor Nanson concludes with two appendices In the first he describes in detail the operation of parotidectomy with preservation of the facial nerve and concludes "It is suggested that all tumours of the parotid gland should be removed by this method of radical anatomical surgery" In the second appendix he describes experiments in which atrophy of the parotid glands of rats was induced by heavy doses of irradiation —up to 8000r—and argues that these observations support the use of irradiation clinically as a supplement to the surgical treatment of salivary tumours

DIAGNOSIS OF INFLUENZA-LIKE DISEASES

MANY different viruses are now known to be responsible for outbreaks of respiratory disease Can these infections be distinguished clinically? Can we for example, differentiate an illness due to influenza-A virus from one due to an adenovirus? This question has been explored, but the answers are not yet clear In England Fraser et al [1] investigated influenza-like illnesses in Naval personnel admitted to hospital in the spring of 1959 Most had been infected by influenza A, influenza B, or adenovirus Infections with influenza-A virus preponderated the other viruses each being responsible for only about half as many cases Influenza-B virus was responsible for a higher proportion of cases of pneumonia—20%, compared with 14% for influenza-A virus and 12% for adenovirus Fraser et al were unable to distinguish on clinical grounds alone between infections with the different viruses

On the other hand Schultz et al [2] in the U S A, working similarly with Naval patients in hospital were able to distinguish the clinical picture due to Asian influenza virus from that due to adenovirus infection In the summer of 1957 they studied 112 cases of influenza due to Asian type A, 64 cases of adenovirus infection and 34 cases of unknown ætiology The patients in this third group had diseases resembling influenza but with a higher incidence of pneumonia, this group was almost certainly not homogeneous and contained infections caused by several different organisms

These studies, and similar ones among Air Force personnel, suggest that prolonged combined clinical and ætiological investigations may provide enough experience to enable us to recognise from the symptoms of groups of patients what sort of virus is responsible for an epidemic of respiratory disease In the case of any single patient, however it will probably never be possible to guess the causal organism from the clinical picture

So far the investigations have usually concerned special groups of people—schoolboys soldiers sailors and airmen Equivalent studies should be undertaken on the common outbreaks in the homes of ordinary citizens There is a case for establishing permanent observation-posts whose main duty would be to characterise every epidemic that visited the area Only in this way will it be possible to accumulate the evidence from which to form a reliable conception of the biology of all the organisms that are leading their lives at our expense and continually disturbing the community life around us

DOMESTIC WORK IN HOSPITALS

THERE was a time when most of the duties of a probationer nurse were those of an overworked and underpaid domestic servant Nowadays over £17 million is spent on domestic work in hospitals in England and Wales—and this figure takes no account of similar work done by portering staff and ward orderlies Economic and social changes since the war have made the recruitment of domestic staff of whom there are over 50,000, difficult, but a report from the Ministry of Health [1] shows that improvements are sometimes possible without increased numbers and at little or no additional cost It is based on surveys made in National Health Service hospitals, supplemented by information from industrial and commercial concerns The aims of the inquiry were those of time-and-motion study in industry—to find the volume and type of work done, the best way of doing it, the number of staff required, and (most important of all) the best ways of ensuring that nurses shall be free to concentrate on caring for the patients

80% of the time spent on domestic work in hospitals is taken up on four tasks—30% of the time on cleaning and polishing floors 15% on washing and scrubbing floors and walls, 10% on dusting and polishing furniture and fittings, and 25% on washing up crockery

To be hygienic there is no need for floors to have a mirror-like surface, in fact, such floors, particularly if of thermoplastic tiles may be dangerous to both patients and staff The need for polishing wood and cork floors, and some types of linoleum may be eliminated by the use of plastic floor seals which are non-slip and do not need waxing In any event, some experts think that floors need be polished only three to five times and then merely to preserve the surface The tradition of polishing floors at least once a week is better forgotten When floors have to be polished, the report recommends the use of power-driven machines, although the use of such machines for stone and similar floors is seldom justified

For general dusting especially at heights above eye level vacuum-cleaners of cylinder type are recommended Electric-light fittings often form dust-traps and are equally often neglected It is suggested that these should be the responsibility of the engineering or portering staffs rather than that of the female domestic staff

Washing-up machines do not offer such advantage as may appear at first sight much of the time wasted on washing up could be saved by intelligent planning on the lines laid down in a Government booklet *Clean Catering* [2] The use of drying cloths is deprecated because they are a potent source of infection, washing-up water should be sufficiently hot (at least 170 F, or 77 C) for crockery to dry rapidly on its own

The report cites instances of wasted effort—such as the time spent in polishing odds and ends of metal that would be better painted over and the enthusiasm devoted to the polishing of cutlery—particularly that for the use of senior staff—with unnecessarily large amounts of metal polish Emphasis is rightly placed on the proper cleansing and disinfection of mops brooms, and floor cloths

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[1] Fraser P K Hatch L A Le Clercq L G H Forster, J R *Amer J med Sci* 1960 239 320

[2] Schultz I Gundelfinger B Rosenbaum M Woolridge R DeBerry P *J Lab clin Med* 1960 55, 497

[1] Organisation and Management of Domestic Work in Hospitals Hospital O and M Service Report no 4 London 1960 Pp 30 2s

[2] Clean Catering H.M. Stationery Office 1950

The turnover of hospital domestic workers is high, mainly because of the competition from industry, and the report deals with the non-financial factors which contribute to good relations between management and staff, and includes suggestions for training and supervision Domestic work in hospitals presents many problems, and, as correspondents pointed out last year, many of our hospitals are dangerously dirty This report is a timely reminder that in the control of infection cleanliness is more important, and often cheaper, than polish

DICHLORPHENAMIDE FOR RESPIRATORY INSUFFICIENCY

MUCH can now be done to tide the patient with chronic bronchitis and emphysema over an acute episode of respiratory insufficiency, but chronic hypoxia and hypercapnia tend speedily to exhaust therapeutic ingenuity A favourable report by Naimark et al[1] on the effect of dichlorphenamide in this condition is, therefore, welcome Dichlorphenamide, a new carbonic anhydrase inhibitor with an activity estimated as 30 times that of acetazolamide, was given in a dosage of 200 mg daily for from two to thirty weeks to 15 hospital patients with hypercapnia persisting after intensive routine therapy

11 of these patients had emphysema, 1 had undergone thoracoplasty on account of pulmonary tuberculosis, 1 had kyphoscoliosis, and 2 had pulmonary fibrosis, all had clinical evidence of severe respiratory insufficiency associated with hypoxia and hypercapnia With 1 exception these patients claimed to have less dyspnœa, greater effort tolerance, and a feeling of well-being while receiving the drug Clinical improvement was associated with favourable changes in arterial gas tensions there was pronounced reduction in hypercapnia in every patient but 1 (mean decrease 10 9 mm Hg) and a consistent rise in oxygen tension (mean increase 16 3 mm Hg) Side-effects were absent, except for transient nausea in 2 patients and severe headache in 1 Withdrawal of the drug was followed by clinical deterioration, increased hypercapnia, and hypoxia, and further administration by clinical recovery and more favourable arterial gas tensions The alveolar oxygen tension rose in 7 out of 9 patients studied, and this change was accompanied by a rise in arterial oxygen tension although in 5 of these subjects the alveolar-arterial oxygen gradient increased on the other hand, in 2 patients the arterial oxygen tension rose although the alveolar oxygen tension did not, so that in these the alveolar-arterial oxygen tension gradient decreased Alveolar ventilation was increased in the 7 patients with a rise in alveolar oxygen tension the mean increase was 0 67 litre per minute, and the mean increase in minute ventilation was 0 6 litre per minute The respiratory rate tended to slow and the tidal volume to increase

Significant diuresis during dichlorphenamide therapy was noted in only 2 patients, and the arterial pH after an initial fall tended to return to the control level The effect of the drug on water and electrolyte excretion was specially studied in 3 patients In 2 receiving the standard ward diet, administration of the drug resulted in significant diuresis with an increased output of sodium, potassium, and chloride associated with a fall in arterial pH, serum-bicarbonate, and serum-sodium and, despite the chloruresis, a rise in serum-chloride The other patient was put on a fixed sodium-chloride intake, and here there was transient diuresis, an increased output of sodium and potassium, and very slight chloruresis, there was a fall in serum sodium and potassium and in arterial bicarbonate, a rise in serum-chloride, and a gradual rise in arterial pH to the control level after an initial fall

Naimark et al point out that the reduction in arterial carbon-dioxide tension during dichlorphenamide therapy could be accounted for by increased alveolar ventilation, decreased tissue carbon-dioxide production, or a combination of these factors Alveolar ventilation did, in fact, increase in most patients, and, although changes in carbon-dioxide elimination or oxygen consumption were not observed, Naimark et al do not exclude the possibility that they may have been present The hypothesis of decreased tissue carbon-dioxide production is supported by the evidence that acetazolamide decreases the metabolic rate in rats[2] Although the resting ventilation increased during dichlorphenamide therapy, the ventilatory response to inhaled carbon dioxide in 3 healthy and in 3 emphysematous subjects did not indicate heightened sensitivity of the respiratory centre to changes in arterial carbon-dioxide tension But in dogs acetazolamide has been found to decrease elimination of carbon dioxide by increasing the body carbon-dioxide stores[3], and Naimark et al suggest that, owing to the carbonic-anhydrase-inhibiting effect of dichlorphenamide, the carbon-dioxide tension in the tissues and in the respiratory centre may actually have been higher than it was before treatment, thus accounting for the increased ventilation and the lowered arterial-blood level They do not consider that relief of pulmonary congestion as a result of diuresis is likely to account for the improvement in gas tensions, for a significant diuretic effect was not demonstrated in most patients who were notably benefited by treatment

Further investigation is obviously needed to determine exactly how dichlorphenamide works, but meanwhile the results of this interesting study strongly suggest that it will prove valuable in the management of chronic respiratory insufficiency

HEALTH AND PRACTICE

Darbishire House is six years old, and without further description doctors throughout the world identify this active youngster as the child of Manchester University and the city of Manchester A new pattern of medical care is being developed in centres such as this where practice, without (it is hoped) losing its personal character, is being adapted to the advances of the present day At Darbishire House the general practitioner can work to the same standard of efficiency as his hospital colleague, and he can teach this standard to others The student is taught that the practitioner's responsibility is towards the whole person—indeed the whole family—and that where he cannot himself fulfil this responsibility he should do so through the special skills of others who work with him A full-time social worker is based on the Manchester unit, and the district nurses and midwives are also members of the practice team in whose work prevention and therapy merge

If the idea of integrated preventive and therapeutic health care based on general practice is now accepted, the methods by which this is to be achieved are still far from settled In centres such as Darbishire House different methods can be tested Further operational research into the activities of general practitioners is urgently needed both in health-centre practices and in those of conventional type The universities of Manchester, Edinburgh, and Bristol, each of which has developed its teaching health centre in its own way, have shown that the partnership between don and practitioner can be fertile Others might usefully do the same

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[1] Naimark, A , Brodovsky D M , Cherniack, R M *Amer J Med* 1960, 28, 368

[2] Tenney, S M, Tschetter, A B *Amer J med Sci* 1959, 237, 23

[3] Muthoefer, J C *J appl Physiol* 1959, 14, 109

Special Articles

THE PREVENTION OF TETANUS*

G. E. FULFORD
M.B. Lond.

ACTIVE immunisation with tetanus toxoid was introduced twenty years ago. It was used extensively during the 1939–45 war and reduced the incidence of tetanus in the American army to 6 cases per million injured. The corresponding figure at the end of the 1914–18 war, using anti-tetanus serum, was 1000 cases per million injured (Barr and Sachs 1955).

In England and Wales there are now about 200 cases of tetanus every year, and in 1957 the number of deaths was 28 (Registrar General 1958). The case-mortality has steadily fallen from about 50% in 1931–41 to 27% in the past ten years. The number of deaths is highest in boys aged five to fourteen years, and most of them are in rural areas, particularly in East Anglia and the south-west (*British Medical Journal* 1955).

Moynihan (1956) estimated that in 15% of cases of tetanus the original injury was trivial, while in 35% it was unknown. Hence even the most careful use of anti-tetanus serum, given prophylactically, could prevent only half the cases—or perhaps less, because occasionally elimination of serum is increased (Barr and Sachs 1955) and tetanus may then occur in spite of its administration (Littlewood et al. 1954).

TABLE I—DISTRIBUTION BY AGE-GROUPS OF MALES AND FEMALES IN THE SURVEY

Expected distribution in parentheses (Registrar General 1958)

Age-group	Males	Females	Total
0–4	61 (*54*)	28 (*20*)	89 (*74*)
5–9	122 (*58*)	73 (*25*)	195 (*83*)
10–14	114 (*49*)	48 (*20*)	162 (*69*)
15–19	86 (*43*)	19 (*19*)	105 (*62*)
20–29	98 (*90*)	24 (*39*)	122 (*129*)
30–39	85 (*99*)	37 (*43*)	122 (*142*)
40–49	64 (*104*)	31 (*45*)	95 (*149*)
50–59	24 (*87*)	19 (*40*)	43 (*127*)
60–69	23 (*60*)	20 (*32*)	43 (*92*)
70–	13 (*46*)	11 (*27*)	24 (*73*)
Total	690	310	1000

TABLE II—INCIDENCE OF DIFFERENT TYPES OF WOUNDS

Actual numbers in parentheses

Classification of injury	Males	Females	Total
Superficial	37% (*258*)	44% (*135*)	39·3% (*393*)
Deep	55% (*380*)	46% (*143*)	52·3% (*523*)
Penetrating	8% (*52*)	10% (*32*)	8·4% (*84*)
Clean	70% (*482*)	78% (*242*)	72·4% (*724*)
Dirty	30% (*208*)	22% (*68*)	27·6% (*276*)

Active immunity is produced by subcutaneous injection of three 1 ml. doses of tetanus toxoid, the second six to twelve weeks after the first. Immunity develops a few days after the second injection, but a third is required six to eighteen months later. Thereafter immunity can almost always be maintained by a booster dose of 1 ml. every five years. After wounding, a booster dose should be given unless the injury has occurred within six months of the second injection or within eighteen months of a third or booster dose, when the patient will be covered by the immunity from the last injection.

Survey

The object of my survey was to ascertain how the benefits of immunisation can best be given to the public. It was made in the casualty department of Putney Hospital where, within four months, 1000 patients were seen who had a breach of epithelium (not caused by burns). These formed the survey group (tables I and II).

Previous Prophylaxis

When the patient had had prophylactic treatment more than once, only the latest injection was recorded, except when serum had been given after active immunisation (table III).

156 patients (121 males and 35 females), or 16% of the series, had had serum. 175 (18%) had been actively immunised while in the Forces: of these only 3 were women and 104 had been immunised ten or more years previously. 14 had subsequently been given serum. Only 50 patients (5%), of whom 7 were females, had received tetanus toxoid outside the Forces.

TABLE III—PREVIOUS ANTI-TETANUS PROPHYLAXIS

—		1958	1957	1956	1955	1954	1953	1952	1951	1950	1949	1948–43	1943–	Total
Anti-tetanus serum	Male	17	30	24	13	10	6	3	1	4	1	7	5	121
	Female	1	12	3	3	1	4	3	3			2	3	35
Tetanus toxoid in Forces	Male		7	17	19	5	3	4	3	3	7	97	7	172
	Female			1				2						3
Tetanus toxoid from other sources	Male	25	8	5	2	2				1				43
	Female	3	3				1							7

10 children had had toxoid as part of their immunisation in infancy, while 1 had had it before going abroad with his soldier father. An ex-employee of the Southern Gas Board had been immunised while in the board's service. 2 men had been immunised in hospital as part of their treatment. One American lady had been immunised before starting on her tour of Europe. An Englishman was also seen who had been immunised before travelling abroad. The remaining patients had all received toxoid in a casualty department. 16 patients had had boosting doses (10 elsewhere and 6 at Putney Hospital), while 18 had received their first dose of toxoid at Putney (13 during the survey) and returned with a second wound.

Treatment

As part of the treatment every patient received some form of anti-tetanus injection unless he was covered by active immunisation or refused the injection (7) or was being immunised against poliomyelitis (20) (table IV). 19 of those who were held to be covered had been immunised in the casualty department of Putney Hospital as part of the treatment of a previous wound.

Anti-tetanus serum was given whenever there was much risk of tetanus—usually for penetrating wounds incurred out of doors. Before patients were given the full dose of serum they always had a test dose, and if this produced a general or local reaction the case was reassessed. Serum was not given to any patient who had had it previously.

94 test injections of serum were given with no general reactions, but 1 boy had a local reaction and did not receive the full dose, being actively immunised instead. The remaining 93 had full doses of serum with no immediate reactions, but 5

TABLE IV—ANTI-TETANUS PROPHYLAXIS GIVEN IN SURVEY

Treatment	Males	Females	Total
Serum test dose	54	40	94 (*9·4%*)
Serum full dose	53	40	93 (*9·3%*)
1st toxoid	412	259	671 (*67·1%*)
2nd toxoid	195	125	320 (*32·0%*)
	15 elsewhere	10 elsewhere	25 elsewhere
Booster toxoid	187	6	193 (*19·3%*)
Refused	7		7 (*0·7%*)
Receiving poliomyelitis immunisation	15	5	20 (*2·0%*)
Actively immune	25	4	29 (*2·9%*)

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* From a paper successful in the South West Metropolitan Regional Hospital Board's competition for research report, 1958.

patients had a local reaction between the fourth and eighth day In 1 this became a generalised urticaria which was only controlled with anti-histamines six weeks afterwards The incidence of local reactions was therefore 6%, which agrees with the findings of Moynihan (1955) 14 of these patients returned for active immunisation, including 5 of the 6 who had had reactions

The remaining patients received tetanus toxoid For those who had been actively immunised previously this was a boosting dose Those for whom it was a first injection were given a form telling them that they would require a second injection in six weeks When they attended for this they were given a record of the immunisation

Of 671 receiving a first injection 320 (52%) returned for the second 35 said they would get their second injection elsewhere In 4 cases there were local reactions to toxoid but these were less severe than the serum reactions Of the wounds treated, 452 were sutured and 60 patients were given antibiotics

Discussion

Because tetanus may follow trivial wounds, it cannot be completely prevented by a policy of passive immunisation

This is vividly illustrated by a case at Putney soon after the end of the survey An elderly lady sustained a small laceration of her leg while out in her garden on Guy Fawkes night She would probably never have been seen except that the wound involved a varicose vein and bled excessively Elevation of the leg stopped the bleeding and the laceration was treated by local toilet and dressing A week later she was admitted with tetanus

Tetanus can be eradicated only by active immunisation of the population This is a formidable undertaking, but the survey shows how it can be done

At Putney about a fifth of the public had already been actively immunised at some time, mostly in the Forces Half of them, however, had been inoculated ten or more years previously, and after this time probably only about 60% of people have enough antibodies to prevent tetanus On the other hand 99% will still respond to a boosting dose of toxoid and can produce an adequate antibody response by the thirteenth day (Peterson 1955) When treated for any wound, these people should always be given a boosting dose of toxoid

14 patients had elsewhere been given serum though they had a history of active immunisation In 3 of these cases (1 treated at a teaching hospital) serum had been given within three years of active immunisation If a patient had died from one of these serum injections a charge of negligence might have been made

Now that National Service is ceasing, the principal source of active immunisation will disappear, and the active immunity of the population will decrease Some efforts are being made on behalf of certain sections For example, many independent schools are immunising their children (Morley 1958, Scott 1958) and the Southern Gas Board offers active immunisation to all men employed on mains or service-laying gangs (Carson 1958) But, though such arrangements should be encouraged, their effects are small in relation to the population as a whole

Another source of active immunity is immunisation of infants with combined antigens Tetanus has been combined with diphtheria and pertussis, so that immunity to all three can be produced by three injections at monthly intervals But most of this work is done at welfare clinics, which, on advice from the Ministry of Health (1957), have been giving each immunisation separately, because of the possible greater risk of poliomyelitis after the use of combined antigens (Medical Research Council 1956) In its first year a baby is thus given a large number of prophylactic injections of which tetanus is left until last—by which time the mother as well as the baby are tired of the needles, and tetanus immunisation is not performed

The effect of this policy is shown in the survey, for, whereas about three-quarters of the children under ten years of age had been immunised against diphtheria or pertussis, only 6 patients, 1 of whom was Danish, had received combined antigens If all these children had been given combined antigens, the number of actively immune patients in the survey would have been doubled That infancy is the right time for tetanus immunisation is confirmed by the fact that our patients with wounds included four times as many young people (aged between five and nineteen) as the general population (table I), and the highest death-rate from tetanus is in boys aged five to fourteen Lately, because of the increase in the number of immunising injections, clinics in some areas have begun to use combined antigens

A further opportunity for active immunisation is in casualty departments Already some departments are offering active immunisation to people who have been given anti-tetanus serum (Gardner et al 1958, Randall 1958) In this survey, by giving toxoid to every patient who did not need serum, and by offering active immunisation after serum prophylaxis, 320 people were actively immunised, returning for their second injection A very rough estimate of the population served by the Putney Hospital casualty department is 50,000, which means that about 0 5% of them were immunised in four months If this policy was applied to the whole country 1 5% of the population would be actively immunised each year, and in adding these to the number already immune we should have gone a long way towards our aim of active immunity for everybody

That this use of toxoid is worth while is shown by the fact that in these four months no fewer than 13 patients returned with fresh injuries, having been actively immunised earlier in the survey

The main objection to active immunisation is that people rarely know the details of their previous immunisations, and without this information a doctor cannot know whether a patient will be protected immediately by a further single injection of toxoid One answer to this is that everybody should carry a record card Admittedly cards are lost, and not carried when required, and, as Kup (1958) pointed out, they would have to be made of a " highly durable and synthetic plastic " if they were not to wear out These difficulties could be overcome by a central records department, which would maintain duplicates, but probably the cost will prevent this for many years In this survey the only person who carried a record card of immunisations was an American

This survey shows, I suggest, that in a given area tetanus can be best prevented by using only tetanus toxoid To be effective this policy requires the cooperation of all medical practitioners and would perhaps need to be adopted at regional-hospital-board level

Toxoid should be given to all infants, and also whenever a doctor (general practitioner or casualty officer) sees a patient with a breach of epithelium A large section of the unprotected population will thus become actively immune and will be protected against tetanus following any injury Moreover the immunity of those already immunised will be maintained

Such a policy would reduce the morbidity from serum reactions Eventually it would also abolish the need for record cards, because a history of previous injury or "anti-tetanus" injection would always imply the use of toxoid

Meanwhile there will be a period when the number of people who have had toxoid will be rather small This can be covered by giving toxoid to everyone who has, or may have, previously had any type of anti-tetanus injection (At present these are about 40% of the population) If it is certain that the patient has never previously had any such injection, then, on the merits of the injury, the doctor decides whether to give anti-tetanus serum or not If he decides not to do so, the patient is given toxoid and should attend for a second injection in six to twelve weeks' time All patients given serum are offered active immunisation six weeks afterwards As an increasing proportion of the patients will have had an anti-tetanus injection of some kind, serum will be given less and less often prophylactically

Summary

As a means of prophylaxis, anti-tetanus serum is unsatisfactory because it will never be used for all trivial wounds and because it can itself cause illness and occasionally death

In a patient who has previously had serum, a prophylactic dose of serum may be ineffective

All patients who have had serum should afterwards be actively immunised with toxoid

In this country about a fifth of the population at risk have already been actively immunised, and this proportion could be rapidly increased by the general use of combined prophylactics for infant immunisation The active immunity of the population could then be maintained by the general use of toxoid in casualty departments

The need for recording immunisations can be overcome by adopting a standard procedure for all patients on wounding

1 All patients who have previously had an anti-tetanus injection of any type are given tetanus toxoid

2 If the previous injection was serum or inadequate primary active immunisation, the patient is asked to attend for a second injection of toxoid six to twelve weeks later

3 Patients who have never had any anti-tetanus injection can be given serum or toxoid at the doctor's discretion Afterwards they should be actively immunised by further injections of toxoid

This procedure would very rapidly eliminate the prophylactic use of serum and produce a high level of active immunity in the population

I would like to thank the other casualty officers and the nurses of the casualty department for their help with this survey

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Occasional Survey

DIAGNOSTIC ENZYMOLOGY

SERUM-ENZYME levels are being determined increasingly often as an aid to diagnosis In disease raised levels are occasionally due to release of these substances into the bloodstream from dead or damaged cells Last year in a symposium on diagnostic enzymology the clinical significance of serum-alkaline-phosphatase [1] serum-acid-phosphatase [2] serum-transaminases,[3] and plasma-amylase[4] was discussed

ALKALINE PHOSPHATASE

Robison's [5] discovery of alkaline phosphatase in bone stimulated investigation of the effect of skeletal diseases on the serum-alkaline-phosphatase Raised levels were demonstrated in Paget's disease, hyperparathyroidism, rickets, osteomalacia, osteosarcoma over-productive of bone, and carcinoma with widespread skeletal metastases which are predominantly osteoplastic It was soon realised that in each case the increases were associated with increased activity of osteoblasts In Paget's disease the level tends to rise slowly with extension of the disease and more rapidly when osteogenic sarcoma develops Differentiation of Paget's disease from the osteoplastic metastases of prostatic carcinoma is not aided by determining serum-alkaline-phosphatase since high values are common to both In hyperparathyroidism the level is usually raised but it may be within normal limits The skeletal origin of the surplus serum enzyme is indicated by the fact that on removal of the parathyroid tumour the serum-alkaline-phosphatase level remains raised for a time, and may even rise further, before subsiding gradually over many months as bone repair slowly comes to a halt In rickets due to malnutrition, the increase in the serum enzyme is usually the first index of active disease and is more sensitive than clinical or radiographic examination The serum-alkaline-phosphatase level is usually normal with healing fractures, in osteopetrosis, and in generalised osteosclerosis due to chronic fluorine poisoning It is usually normal, but may be increased, in other forms of osteosclerosis and in fibrous dysplasia of bone Diseases characterised by osteoporosis or bone destruction are associated with normal serum-alkaline-phosphatase activity a typical example is multiple myelomatosis

In some diseases the serum-alkaline-phosphatase level may be lower than normal Low levels are found with arrest of growth—for example, in achondroplasia or cretinism The level is low also in scurvy and after exposure to radioactive substances which are deposited in the bone [6] Hypophosphatasia [7] is an interesting clinical syndrome due to an inborn error of metabolism characterised by deficiency of alkaline phosphatase in bone, kidney, intestinal mucosa, liver, leucocytes, and blood-plasma The syndrome is dominated by abnormal mineralisation of bone which may result in profound skeletal changes closely mimicking vitamin-D-resistant rickets

Alkaline phosphatase is probably excreted mostly through the biliary tract[8] It is, therefore, not surprising that both intrahepatic and extrahepatic obstruction of the biliary tract are associated with a rise in the serum level Thus a rise is found in space-occupying hepatic lesions, such as metastases and abscess, in granulomatous and infiltrative diseases of the liver, such as sarcoidosis, tuberculosis, Hodgkin's disease, and amyloidosis, in drug-induced hepatotoxicity of the cholestatic type (such as is caused by arsphenamine and chlorpromazine), and in obstruction due to biliary cirrhosis There is a larger obstructive element in viral hepatitis, but in the majority of patients with this disease the increase in serum-alkaline-phosphatase activity is distinctly less than is usual in obstruction of the extrahepatic or intrahepatic biliary tract This has not yet been satisfactorily explained

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[3] Wróblewski F *ibid* p 911

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ACID PHOSPHATASE

As regards serum-acid-phosphatase,[2] a cardinal feature is that adult human prostate contains up to 1000 times the activity of other tissues, but this high activity does not appear until puberty In health the serum contains a small but significant amount of acid phosphatase of unknown, non-prostatic, origin, but the amount is greatly increased in the majority of men with metastases from prostatic carcinoma, in whom the level falls sharply within three or four days after surgical castration or within two weeks after the institution of œstrogen therapy Patients whose acid phosphatase does not decrease significantly during endocrine therapy fail to remit clinically The serum level rises irrespective of whether metastasis has taken place to bone or to the soft parts The most probable explanation of these findings is that the intact gland contains barriers which ordinarily prevent escape of the enzyme into the circulation, but when metastasis takes place these barriers are no longer present and the prostatic secretion enters the blood About a quarter of untreated patients with disseminated disease have no clear-cut increase of serum-acid-phosphatase

In health, acid phosphatase activity is about the same in the serum of women as in that of men Likely sources of the enzyme normally present in the blood are liver, red blood-cells, and blood-platelets Obviously, therefore, acid phosphatase from diseased tissues besides the prostate may enter the circulation in measurable amounts Raised serum levels have occasionally been reported in cases of Paget's disease of bone, of metastases, and of hyperparathyroidism, and the level is often raised in Gaucher's disease[9] It is therefore important to differentiate acid phosphatase derived from the prostate from that derived from other tissues This is done by means of differential inhibition Ethyl alcohol and *l*-tartrate apparently have a rather selective inhibitory effect on prostatic acid phosphatase and little effect on the acid phosphatase of erythrocytes, the reverse is true of cupric ions and formaldehyde, which inhibit erythrocyte phosphatase notably, but prostatic phosphatase very little Using acid phosphatase inhibition by *l*-tartrate, Fishman et al[10] have demonstrated increases in prostatic acid phosphatase in the serum of healthy men after massage of the gland Accordingly, examination of the serum for this enzyme should not be preceded by manipulation of the prostate either manually or by catheterisation It seems that some 6% of healthy men have transitory rises in serum acid phosphatase inhibited by tartrate,[11] and thus a slight rise is not a reliable index of prostatic cancer unless it is shown to persist

TRANSAMINASES

Wroblewski,[3] discussing serum-transaminase determinations in the diagnosis of ischæmic heart-disease,[3] [12] points out that a rise in serum-glutamic-oxalacetic-transaminase (S G O T) activity above 300 units, at the peak after infarction, indicates a poor prognosis After myocardial infarction a rise in S G O T activity is not influenced by, or correlated with, heart-failure uncomplicated by liver disorder, location of the infarction, administration of digitalis or quinidine, age, sex, colour, body-temperature, erythrocyte-sedimentation rate, leucocyte-count, or urinary output When the electrocardiogram is not diagnostic of myocardial infarction or is obscured by previous myocardial infarction, bundle-branch block, Wolff-Parkinson-White syndrome, or other electrocardiographic aberrations, a rise in S G O T activity in a clinical setting suggestive of infarction is especially helpful in diagnosis Secondary rises have been observed in patients who, following acute myocardial infarction, show clinical features consistent with extension of the infarct With regard to hepatic disease, ambulation during recovery from infective hepatitis is sometimes associated with a *small* rise in serum-transaminase, if the rise is 50 or more units, return to rest is recommended[13] Deviations from the usual pattern of serial alterations in S G O T and serum-glutamic-pyruvic-transaminase in the course of acute infective hepatitis suggest associated complications, relapses, or chronicity of the hepatic lesion Apparently the serial and quantitative changes in the serum-transaminases during the course of hepatitis reflect the clinical state more accurately than do the usual tests of liver function The S G O T activity has been reported to be as sensitive an index of primary and metastatic cancerous involvement of the liver as the serum-alkaline-phosphatase,[14] but S G O T is unaffected by the presence of active metastatic cancer

Surgical trauma to skeletal muscle has also been observed to result at times in increases of serum-transaminase[15], and the degree of muscle trauma seems to be related to the peak rise in S G O T The serum-enzyme activity cannot therefore be used as a valid index of cardiac injury in accident victims Of neuromuscular diseases, the S G O T level is raised in progressive muscular dystrophy, pseudohypertrophic muscular dystrophy, and dermatomyositis Amyotrophic lateral sclerosis, progressive muscular atrophy, myæsthenia gravis, rheumatoid musculoskeletal diseases, and nerve section are not associated with increased serum-transaminase activity

AMYLASE

With regard to plasma-amylase,[4] the evidence suggests that the activity in normal plasma is derived from various sources of which the chief are the salivary glands, the pancreas, the liver, striated muscle, adipose tissue, and fallopian tubes The contribution of the pancreas is probably much smaller than has generally been supposed Neither an increase in volume flow of pancreatic juice nor stimulation of pancreatic enzyme production will of itself increase serum-enzyme concentration. The important determinant is elevation of intraductal pressure. In pancreatic disease, therefore, two pathological features in the pancreas influence the height to which the amylase rises: (1) continued secretion against obstruction, and (2) the disruption of acinar cells and ductular apparatus. Because variables, including renal clearance, are involved no straightforward correlation may exist between the amylase content of any one sample of serum and the severity of acute pancreatitis, but in one series it was found that all patients with values of over 900 units did have pyrexia and pronounced leucocytosis. The rise is usually transient, often lasting only three or four days, but it has been found to persist for up to three weeks, and such persistence, when the patient is on a good therapeutic regime, indicates a complication such as abscess or pseudocyst with continuing inflammatory changes.[16] The situation is further complicated by the fact that an increase in serum-amylase level may result from administration of morphine or codeine. Rises, sometimes quite high, have also been noted in perforated peptic ulcer, not necessarily involving the pancreas, and in intestinal obstruction. A rise often follows abdominal operations particularly for upper abdominal conditions, and rupture of an ectopic pregnancy.

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OTHER SERUM ENZYMES

Other serum-enzyme determinations are of value in clinical diagnosis.[17] Glucose-6-phosphatase is very low in glycogen-storage disease and is raised in hepatitis and cirrhosis. Aldolase is diminished in progressive muscular dystrophy; it is raised after liver disease and myocardial infarction, and, fairly commonly, in cancer. Phosphohexose-isomerase is raised in progressive muscular dystrophy, after myocardial infarction, and in hæmolytic anæmia, carcinoma of the prostate, and carcinoma of the breast. Phosphoglucomutase has been shown to be raised in cancer and during hepatitis. Lactic dehydrogenase and malic dehydrogenase are both raised after myocardial infarction,[18] and the elevation tends to persist much longer than that of S.G.O.T. Lactic dehydrogenase is also raised as a result of hepatitis, muscular dystrophy, and carcinomatosis. Isocitric dehydrogenase is raised in liver disease but remains normal after cardiac infarction. Plasma-pseudocholinesterase is diminished in liver disease, whereas the true cholinesterase of the erythrocytes is much lowered in insecticide poisoning with organophosphorus compounds. Serum-cæruloplasmin is usually much diminished in hepatolenticular degeneration.

Public Health

Vaccination Against Poliomyelitis

THE Ministry of Health reports that by the end of March nearly 13,200,000 people in Great Britain had received at least two vaccinations against poliomyelitis; over 9,400,000 of them had had the course of three injections. The estimated acceptance-rate for children (1943–59 group) was 75.5% and for young adults (1933–42) 48%. The extension of vaccination to cover all persons under 40, announced by the Minister in February, has so far aroused little response.

In England Now

A Running Commentary by Peripatetic Correspondents

Is there a meteorologist among our peripatetic band, circumambulating the cloisters with an occasional glance at the weather-vane or the "twelve winded sky"? Is there a weathercaster in the house? If so, will you ask him to tell us what has happened to April? A week or so ago we had her last day. She cannot come again for nearly eleven months and I don't believe she'll come then. She doesn't. This year she put her head in at the window for half a day but was gone before evening and that is about the most I've seen of her for years and years. Yet, over the centuries, she must have been pretty constant in her inconstancy. Chaucer, Shakespeare, an anonymous madrigalist who saw her "in his mistress' face", William Watson who found her girlish some sixty years ago—all took it for granted that everyone knew her endearing ways, they had only to mention her name. We all did know her, she was "just like they said", until when? Twenty years ago, or less or more? Whenever it was she just stopped coming. Her month might be cold or warm, bright or dull, possibly even wet, but the "showres sweete", the "uncertain glories", the "girlish laughter and girlish tears" were gone. In 1960 her month ended sunnily enough but with a Nor'-by-East wind that didn't let up for ten to fourteen days and the ground as dry and hard as a bone. "Pierced to the root" my foot! What is it? Melting polar ice? Electronic intoxication in the perisphere? I do hope someone can tell us. Of course what I really wanted to know is: shall I see her again and will my grandchildren ever see her at all? She was a pretty minx and good for the garden, too.

* * *

To my right in the general surgical ward lay an Italian. He had lived in this country for many years before the war, but had returned to Italy in 1939 and had fought against us. "Come over here from the Continent", said the man who was later to prove himself the curator of unreliable ward information, "to have his prostate out on the cheap." To my left was a disgruntled Anglo-Saxon who had seen better days. "But for this Welfare State nonsense I might still have the wherewithal to afford private treatment in a nursing-home." A few beds away to the left was a surgical-instrument maker. His conversation was largely about his work and his delight in it. With a grin he told me that he himself had made the instrument which the surgeon would be using to close the hole between his bowel and his bladder.

Opposite me was a retired banker who was also the author of a successful book on cookery. Closer contact with him and a description of his sufferings in and out of hospitals over the previous five years helped me to understand why, regardless of money, he chose to be in a public ward. His lively and sincere interest in the welfare of his fellow patients helped him in his own afflictions. He loathed the thought of being alone with his pain and was largely responsible for the air of cheerfulness which pervaded the ward. Alongside the banker was a bright, well-mannered boy of 15 with an undescended testicle. He informed me in confidence that he was one day going to be the Astronomer Royal. At the circumference of my immediate circle was a barrow boy—a true Cockney. I shall long remember the face of the medical student who, when apologising for his heavy-handedness in removing a dressing, was met with "Don't worry, cock. I'll ave yer selling nylons wiv me in the Old Kent Road when they chucks yer out of 'ere."

* * *

I remembered that a faithful attender at my follow-up clinic had bought a new car, and asked whether it was satisfactory. "Fine," he said, "But I've had to have the heater dismantled already, and it still isn't right." I sympathised. "You see it kept splashing white spots on my trouser legs." Once more I nodded absentmindedly. "They took it out, said there was nothing wrong and now it's hotter than ever—but it still splashes me " Then I woke up, and as I tested his urine and found it loaded with sugar, I wondered whether car-accessory firms could use this in their advertisements " Diagnose your Diabetes with SUDH—our Supa-Urina-Drya-Heata " No doubt they wouldn't report sugar ++, but just wotalotugot

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* * *

Entia non sunt multiplicanda præter necessitatem had been taught to us as students, when we all had thought the first four words were the ones that mattered It wasn't for years that I learned to respect *præter necessitatem* the most In Singapore I had seen Chinese with tuberculosis, syphilis, amœbiasis, and worms—and then realised that they hadn't come about any of them, but were brought by their relatives because they were so ill from their real complaint of, perhaps, a pharyngeal carcinoma

I first saw Mr X a few years ago His eye had been removed four years previously for a retinoblastoma, and when he presented with jaundice and an enlarged liver I feared the worst, but he had infective hepatitis and recovered fully Next time he came his wife said he had pernicious anæmia I discounted her story, thinking that secondaries were far more likely—and to my chagrin have been treating his addisonian anæmia ever since Last year he seemed changed He was terribly cold, he told me in a gruff voice, and so constipated and deaf and slow that he was thinking of giving up his job So I added thyroid extract to his medication, and all was well for the time being Last month he came again, and I have already told you about his car-heater, and how it seemed to splash white marks on his legs Now he has diabetes as well, you might suppose that William of Occam could keep quiet for a bit, though I suspect he is saying that the syndrome of retinoblastoma and infective hepatitis and addisonian anæmia and myxœdema and diabetes is just the entity of polygenosis, and why do I insist on multiplying it out ?

* * *

If anything fills me with envy it's people who know things,
Because I haven't a memory in which I can usefully stow things,
But some people, undoubtedly closer than I to reality,
Are never at a loss to itemise and quantify actuality
They invariably have at the tips of their tongues
Not only the surface markings of the longues
(And suchlike information, acquired long ago,
Which any medical man, save me, could reasonably be expected
  to know)
But the most incredible hoarded facts
Such as every provision of the N H S Acts,
The equations of Gaussian distribution
And where are the islands called Aleutian,
The colour-coding of electrical resistors
And which one's whom of the Mitford sistors
And all the Siberian railway gauges
And which damned year Diocletian froze wauges
And so on *
It's really too depressing to go on
While, *form-filling*, I, recalling with effort Age, Address, and
  Nearest Railway Station,
Am stumped for several minutes by Year of Graduation

But, when I consider those general-knowledgeable Joneses,
The thing that I feel, deep down in my bones, is
That largely their informational cupidity
Is explained by an underlying stupidity
Indeed, I tell myself in a way that's smugly self-consolatory,
Intelligence and ignorance are intercompensatory
And it can't be disputed by any philosopher of whom I wot
That if, of information, you haven't a lot,
You can always scrape over life's hurdles with intelligent
  guesswork
(Which, in the long run, involves you in luesswork)
So I pity those poor folk who, seeking for status,
Must fill up with facts 'cause they're poor cerebratus

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* I could ave continue this diatribery
With diligent use of a reference libery

Letters to the Editor

HUMAN RELATIONS IN OBSTETRIC PRACTICE

SIR,—It is hard to see how anyone could possibly detract from the observations and conclusions expressed by Professor Morris—so broadly and humanely are they based

The problem is clearly not due to a few frustrated spinsters who administer barbaric rituals, but is the outcome more probably of factors inherent in obstetric practice itself, which cause the average " normal " midwife and doctor to fail in their personal relationships with their patients

Obstetrics appeals to many because it is a practical specialty productive of a guaranteed end-product far more tangible than the patient's gratitude Unlike medicine and surgery, all the patients suffer from the same " disease ", *they all follow the same natural history, and are subject* to the same complications Such patients tend to become units devoid of identity

Every known obstetric hazard is expressed as a percentage Small wonder then that a practical person working upon stereotyped material, with statistics as his master, seldom allows his imagination to wander above the fundus The very risks which we wish to avoid are the only ones not expressed in figures Patients who develop one-child frigidity, marital estrangements, or varying degrees of depression and fear seldom complain and never die They simply remain " primips "

" Maternal distress " only catches the obstetrician's eye as a rising pulse-rate Even if he does notice something overtly amiss he will not summon expert aid for two reasons In medicine every man is his own psychiatrist He can no more admit to a failure in human relationships than he can admit to being a bad driver Secondly, everyone knows that most psychiatric conditions are incurable The obstetrician, so consistently producing results, forgets that most doctors cannot hope to cure, but only to comfort their patients None the less, when palliation is called for he sends for the radiotherapist Why not the psychiatrist ?

The midwife is subject to the monotony of normal labour without even the occasional abnormal case to leaven the dough. She resents the doctors who " pinch all the best cases ", or " rush in at the last moment to pull the baby out " These feelings communicate themselves

She forgets that the patient is not used to appearing unclothed in an undignified attitude, performing a function akin to defæcation Endless reiteration lays calluses on her emotions When kindness is most needed she is capable only of exhortation Intent on five minutes' juggling at the perineum she overlooks the *fact that, for the patient,* this moment represents a unique end to nine months of anxious waiting

After labour is over the midwife's task finishes where the mother's begins, and when the patient is most demanding of sympathy and explanation she is least likely to obtain it She may even have her baby's weight kept from her to " stop her worrying " The patient's worries at this time are, in fact, like an iceberg, and it requires both imagination and insight to detect the larger submerged portion Worse still, it takes time and patience to dissolve them Such worries should be intelligently anticipated, not dextrously avoided

The cure must lie with the people involved If the obstetricians cannot accept the psychiatrists they must cultivate, as part of their equipment, the psychiatric approach For midwives what is needed is a correct psychiatric training, the temperament to accept it, and the time to apply it

Very little can be done about obstetrics itself There is only one way to have a baby, and most women need help

London, S.E 12 B BLACKWELL

SIR,—No-one could disagree with Professor Morris, but I noted that only once were fathers mentioned I quote "If a husband wants to be with his wife in labour I am certain that we have no right to deny him this experience I actively encourage husbands to be present providing they know what to expect" What provision is there for the prenatal instruction of expectant fathers? I am convinced that the husband's influence is very important and that he, rather than obstetrician or nursing staff, determines a woman's attitude to pregnancy and childbirth Mere attendance at the birth is not enough and in too many cases the wish to attend is engendered by curiosity rather than a desire to participate

It should be possible for the obstetrician to have at least one interview with each expectant father and to organise a short series of lectures, illustrated by colour films, to give the necessary instruction It would be a chance to help those men who, by their ignorance or ineptitude, cause their wives avoidable anxiety In the first stage of labour the husband could keep his wife company and minister to her minor needs More personal contact with the fathers would give both obstetricians and nursing staff a better understanding of both mother and infant Hospitals could then, in this respect, compare more favourably with domiciliary midwifery

Preston NORA WILKINSON

BRETYLIUM TOSYLATE IN THE TREATMENT OF HYPERTENSION

SIR,—We were interested to read the article of Feb 6 by Professor McMichael and his colleagues on the excretion of ^{14}C-labelled bretylium tosylate, the hypotensive drug first described in your columns by Boura et al[1] in 1959 Our experience of a six-month follow-up of 25 patients treated with bretylium for six months has been similar to Professor McMichael's A good control of blood-pressure was obtained in 19 patients, moderate control in 4 patients, and renal failure developed in 2 patients while on therapy It was found that tolerance to bretylium gradually developed in 15 patients, and an initial dose of bretylium 200 mg three times a day was increased after some weeks in some instances to 800 mg or more three times a day In one patient a total daily dose of 3200 mg was inadequate to control the hypertension Chlorothiazide was useful as an additional drug and allowed the dosage of bretylium to be reduced

We found that bretylium was an effective hypotensive agent and reached maximum effect in between three and six hours The side-effects were not prominent although 14 out of 25 in the series complained of a transient stuffiness of the nose 5 patients had rather loose motions and 4 a transient frequency of micturition Bretylium affected the mental state and appeared to have a tranquillising effect, althought in 2 patients the reverse occurred and severe psychotic manifestations developed shortly after initiation of bretylium treatment All patients on previous therapy found a great relief from the severe dryness of the mouth, constipation, and blurring of vision A typical remark was "it's nice to be able to see again" Impotence was a complaint in 1 male patient

However, sudden hypotension of moderate severity was a feature in 5 patients and may have been due to irregular absorption of the drug 2 patients with renal failure were found difficult to stabilise and in one patient 300 mg of bretylium daily was sufficient to produce severe hypotension The 1 death in this series was due to progressive renal failure

The six months' trial of bretylium in 25 hypertensives has established satisfactory control in most cases, but sudden hypotension is a real difficulty and further study in patients with renal impairment is indicated This clinical observation is in accord with the low excretion of ^{14}C-labelled bretylium in renal failure observed by Professor McMichael's team at Hammersmith

It is therefore urged that caution should be advised in the use of bretylium particularly where there is renal insufficiency

St. Helen Hospital,
Barnsley

I MCLEAN BAIRD
I UL-HAQ

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THE HÆMATOLOGICAL CHANGES IN PARABIOSIS INTOXICATION

SIR,—In a preliminary communication (March 26) Dr Gurney and Dr Taylor state "We here report the development in parabiosed homologous mice of a condition resembling that known as the parabiotic intoxication syndrome of rats" In recognition of the numerous investigators who have studied the response in that animal, the condition described would be more properly designated as identical with the parabiosis intoxication syndrome of mice, rather than similar to that which occurs in rats Precisely what is meant by the term "homologous mice" is uncertain, for the C3H and AKR strains are not genetically homogeneous

Studies on parabiotic rats have led us to formulate the hypothesis that the anæmia which occurs in one member of an intoxicated pair and the polycythæmia of its twin are due to a shift of blood from one to the other[1-3] Gurney and Taylor believe their findings to be incompatible with this thesis although they present neither adequate reasons for this conclusion nor an alternative explanation The data which they present, however, merely confirm those obtained by many other investigators who have studied murine parabiosis intoxication, and were utilised by us in deriving a theory to explain the mechanism of the disorder

In the mouse it has been reported that parabiotic compatibility requires the presence of identical alleles at the H-2 locus Thus when a pure mouse is joined to a hybrid derived from crossing the pure strain with another, parabiosis intoxication inevitably ensues and it is the hybrid which becomes anæmic[4]

Further experiments in the mouse have led Eichwald,[5] using criteria quite different from those which in rat studies led us to infer that the hæmatological changes were due to unequal blood transfer, to the same conclusion

In summary the findings are that the anæmia is due neither to hæmolysis nor to depressed erythropoiesis, and the polycythæmia of the twin cannot be ascribed to increased erythropoiesis Neither of these states can be produced in recipient hybrids or pure single animals by repeated injections of blood, spleen, or lymph-node suspensions from a donor of the opposite genetic constitution, even though donors and recipients of differing genotype develop intoxication when joined The combined red-cell mass of pairs remains constant, and when intoxication develops or temporarily reverses, the increased red-cell mass in one partner is balanced by an equal decrease in the twin Eichwald concludes "The data obtained suggest that the symptoms of intoxication are due to a massive shift of red cells from the intoxicated mouse to its partner"

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[1] Hall C E, Hall O *J exp Med* 1956, 103, 263

[2] Hall C E, Hall O *Amer J Physiol* 1956 184, 155

[3] Hall C E Levin W C, Hall O *Proc Soc exp Biol, N Y* 1957, 96, 780

[4] Eichwald E J, Lustgraaf, E C, Strainer, M *J nat Cancer Inst* 1959, 23 1193

[5] Eichwald E J Lustgraaf E C Fuson R B Pfaff J P Jr 4th Tissue Homotransplantation Conference *Ann N Y Acad Sci* 1960 (in the press)

In the absence of adequate evidence to the contrary, we believe this to be the explanation which best fits the available facts

University of Texas,
Galveston, Texas

CHARLES E HALL
OCTAVIA HALL

ADDICTION TO DRUGS

SIR,—It is true that in the United Kingdom an addict may apply to any qualified doctor for a supply of drug but it is entirely inaccurate for Mr Harney to state (May 7) that "we have no opiate problem here because narcotics are freely dispensed by doctors to all askers"

The only "magic alchemy for the control of narcotic addiction" which we possess consists of the regular inspection of all chemists', doctors', dentists', and veterinary surgeons' dangerous-drugs registers, and the fact that drug addicts are treated as patients

In America the addict is regarded as a criminal and as such he avoids treatment and supervision Because the drug can only be obtained there illicitly the price is exorbitant and addicts become traffickers in order to pay for their own supply

In this country drugs are available to the bona-fide addict under the National Health Service provided that there is a satisfactory indication for prescribing them and so long as the patient undertakes to accept treatment of his addiction

Accordingly, there is no equivalent temptation here for an addict to sell some of his drug or endeavour to create addiction in others so as to develop a source of income for his own purchases

America will continue to have a serious drug problem so long as addiction is equated with crime, for criminal vested interests will ensure that there is an increasing number of addicts to swell the fantastic profits derived from the peddling of narcotics

The emphasis must be shifted from punishment to treatment, and the latter should be made available free of charge and without penalties to all addicts

ELLIS STUNGO
Honorary Secretary,
Society for the Study of Addiction

London, W 1

FLUORIDATION

SIR,—Mr Capstick (April 16) implies that the physical suffering and expense attendant upon dental caries is insignificant, and can easily be overcome by fitting everyone with dentures Such a view is indefensible

The report of the Ministry of Health for 1958, part 1, states that the amount of fees authorised by the Dental Estimates Board for 1958 for payment to dentists was £44 million, and that 2,352,000 courses of dental treatment were given to children Nearly ten million teeth were extracted, of which two million were removed under general anæsthetic Much of this misery and expense could be saved by the simple and safe procedure of adding fluoride to the community water-supply

In the Ministry of Health reference note, no 9, of July, 1955, it is stated categorically that there is no scientific evidence whatever that fluoride at a level of 1 part per million has any deleterious effect on the health of adults or children For example, in a community whose water-supply contained as much as 8 parts per million of fluoride, careful examination was made of a group who had consumed this water for a minimum of 25 years, and showed that, apart from mottling of the teeth, no important effect could be found in these people to differentiate them from those in a similar community with a low fluoride content in its water

Very many careful and scientific surveys of a similar nature can be quoted It can be accepted that in the present state of knowledge, fluoridation is absolutely known to be safe, very much safer, for instance, than dental extraction under general anæsthesia

The Central Council for
Health Education London W C 1

A J DALZELL-WARD

THE CARPAL-TUNNEL SYNDROME

SIR,—The correspondence on this syndrome, ending with the interesting views of Mrs Draspa (April 9) on the psychological aspect, point to a multiple pathology for this condition

I have seen several antenatal patients who, in the later stages of pregnancy, had symptoms and signs of this syndrome Some of these patients had toxæmia of pregnancy, with œdema of the fingers and wrists Treatment with hydrochlorothiazide to control the œdema reduced or resolved the symptoms in some patients The condition always subsided after labour and therefore no long-term treatment was required These cases support the idea of nerve compression by tissue œdema at the wrist

Netley Abbey,
Hampshire

B J FOSTER

THE NATURE OF HYPERTENSION

SIR,—In the discussion of the nature of essential hypertension, Dr Morrison and Professor Morris[1] used the systolic blood-pressure distribution curves to analyse "bimodality" We cannot accept their conclusions because we consider that systolic blood-pressure alone cannot be used as a quantitative method to study essential hypertension

It has been clearly established that the systolic pressure is influenced directly by (1) conditions which increase the stroke-volume of the left ventricle, and (2) conditions which increase the rigidity of the aorta As many factors can influence these conditions, the range of variability of systolic pressure is so great, that casual readings can easily be shifted by chance very far from the true mean figures This fact hampers work with systolic figures in clinical investigation, and we do not use systolic scores to analyse results in our treatment of hypertension

The diastolic blood-pressure is the true measure of the arteriolar peripheral resistance—the essential key in the development of hypertension The severity of hypertension is determined by this diastolic pressure[2] [3]

According to Morrison and Morris, their diastolic pressure levels were distributed "continuously", without bimodality The bimodality appears only in the systolic curves As the systolic curve does not truly represent the distribution of blood-pressure in the general population, we can accept only the existence of the unimodality of the diastolic curve

Aguirre Hospital,
University of Chile School of Medicine,
Santiago, Chile

R CRUZ-COKE

PLASMODIUM MALARIÆ IN "NEPHROTIC SYNDROME"

SIR,—I found the preliminary communication by Dr Gilles and Dr Hendrickse (April 9) about a relationship between the nephrotic syndrome and infection with *Plasmodium malariæ* in Nigerian children of particular interest because their pædiatric experience in Ibadan, Nigeria, sharply contrasts with mine in Freetown, Sierra Leone

Their report is based on 48 new cases attending University College Hospital over a period of less than one year In the children's medical ward at Connaught Hospital, Freetown, during the period November, 1955, to September, 1959, I can remember seeing only 3 cases of the nephrotic syndrome in children under 10 years old Malarial parasites, other than *P falciparum*, were virtually non-existent in the Freetown area During the six months from March to August, 1959, of a total of 422 admissions to the children's ward, there were 54 proven cases of malaria, all reported as being *P falciparum* infections

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[1] Morrison S L, Morris, J N *Lancet*, 1959, ii, 864

[2] Perera, G A, Brust, A A, Wilkins, R W *J Amer med Ass* 1958, 166, 648

[3] Cruz-Coke, R *Rev med Chile*, 1958, 86, 438, *Lancet*, 1958, ii, 216

The virtual absence of *P malariæ* and the nephrotic syndrome in Freetown tends to support the theory of the ætiological role of *P malariæ* in the nephrotic syndrome, particularly as the two West African territories of Nigeria and Sierra Leone have so many pædiatric problems in common

Queen Elizabeth Hospital, Aden
F STEPHEN CARTER

THE SHORTAGE OF NURSES

SIR,—I would strongly support Mr Malkin's appeal (April 30) for an urgent approach to the problem of the serious shortage of nurses in our hospitals He suggests a central body consisting of representatives of the Ministry of Health, the hospitals themselves, the British Medical Association, and the Royal College of Nursing to be formed to tackle this problem I agree that this is a sound, long-term view but the problem is too acute for this approach

While agreeing that there are other factors in addition to the question of salary, I am convinced that the root cause of our present troubles is our false sense of values in relation to the hopelessly inadequate remuneration of hospital sisters Mr Malkin quotes the "Alice in Wonderland" example of a hospital sister receiving less salary than a ward orderly may receive with overtime Anyone familiar with hospital routine will know that experienced hospital sisters are extremely valuable members of the medical profession and are really the equivalent of specialists in nursing, as far as the treatment of patients is concerned They should, therefore, be paid for their services They deserve a salary which would allow them to run a car and enjoy other amenities which are worthy of the privileged, responsible posts they hold

At present the maximum salary of a hospital sister after 7 years of service is £820 p a After all deductions she receives less than £30 per month I see no reason why a senior sister should not be paid at least £1200 p a If this were done there would be a genuine worthwhile incentive for suitable candidates to take up nursing as a career

Halifax
GEOFFREY HYMAN

REDUNDANT ALPHABETS

SIR,—We have almost lost sight of Shaw's alphabet in the issues (and dubious arguments) of redundancy G B S would not have objected he himself often started fights on the touch-line to bring spectators to his game But Dr Thomas' last fight (May 14) was so skilful and logical as far as it went that it might draw attention away from the game

His distinction between noise and redundancy was very well made The choice of the word "noise" was not particularly happy, but his meaning is clear and no-one would doubt his conclusion that noise is noxious and redundancy potentially protective Following this up, he points out clearly that redundant letters make a word more specific and therefore less easily confused with other words What happens if we follow this argument to its logical conclusion? The most specific words, and therefore the least ambiguous, would be ideograms, but it is a commonplace that ideographic scripts are accompanied by the highest illiteracy Why is this? There must be some factor other than ambiguity which supports illiteracy Quite simply, it is the total number of sound-signs which have to be learned It may be quite true to say that two highly redundant ideograms cannot be visually confused, but what is the good of that if the meaning of neither is known? Redundancy will certainly protect against errors in transmission but if the signals are not understood there will be no transmission as far as the reader is concerned

It was not lack of redundancy in the script which made it so difficult for 4th-century Japanese to learn to read and write It was having to memorise 40,000 distinct characters In the 8th and 9th centuries the kana syllabary of 48 was introduced, and nowadays more and more is written in the Roman alphabet All over the world when scripts have evolved it has always been in this direction from a highly redundant non-phonetic one to a less redundant phonetic script This was my meaning, though badly put, when I said that occasionally to use the letters "ugh" for the sound "f" as in the word "cough" did not protect against errors in transmission I should have said that such usage might result in nothing being transmitted at all

If future generations forget that "cough" was pronounced "cof" I am afraid that Dr Thomas' jingle is going to fall pretty flat But given a Mandarin who remembers the usage, the joke is most likely to survive the sabotage of posterity's careless type-setters if you write

It wasn't the cough that carried him ough,
But the coughin they carried him ough in

Lee-on-Solent, Hants
A S JARRETT

MERIT AWARDS

SIR,—There is much discussion regarding merit awards to practitioners under the N H S and how this money (£500,000) should be allocated It seems to me this sum should be awarded to private practitioners who for good reasons could not enter the Service and whose livelihood has been seriously curtailed by the N H S The practices of those joining the Service were purchased by the Ministry, but no consideration was given for the harm done to private doctors I say in justice and fairness this sum should be given in compensation to them If legislation is necessary, let Parliament legislate

London, W 1
M W BROWDY

SIR,—Would you permit me a hollow laugh? If 13% available to anæsthetists is contemptuous, is not the proposed 3% to general practitioners insulting?

Writtle, Essex
J TUDOR PEMBLETON

INTERMITTENT POSITIVE-PRESSURE RESPIRATION IN INTRACTABLE STATUS ASTHMATICUS

SIR,—May I thank Dr Buzzard (May 7) for his constructive criticism and reply to his important points about sedation in status asthmaticus?

The three fatal cases mentioned in my paper of April 23 received, respectively no sedation, 5 ml paraldehyde and 150 mg amylobarbitone, chlorpromazine 50 mg and promethazine 50 mg p r n q 6h To the remaining seven (unreported) patients admitted to the Salisbury General Infirmary with status asthmaticus in 1959, high doses of sedatives were often given Three patients had chlorpromazine 50 mg and promethazine 50 mg q 6h from three to five days, another patient received 100 mg each of chlorpromazine, promethazine, and pethidine four times within twenty-four hours of admission

Two patients did not need sedation In one patient, admitted in severe distress with marked cyanosis and able only to talk in gasps, the exhibition of chlorpromazine 25 mg and promethazine 25 mg coincided with circulatory collapse and an absent radial pulse This collapse was relieved by the intravenous injection of 3 ml 1-in-1000 adrenaline over four minutes

Ten of the total of twelve patients with status asthmaticus mentioned social or emotional problems on admission, and three of these patients, one of whom subsequently died, were referred for a psychiatric opinion

Sedation is an integral part of the orthodox management of status asthmaticus (M R C Trials Subcommittee[1])

The first fatal case of bronchial asthma to appear in the literature[2] was a female morphine addict aged forty, who lived long enough to die from congestive cardiac failure induced by her final attack of status asthmaticus

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[1] *Lancet*, 1956, i 803

[2] van Leyden, E *D sch militärärztl Z* 1886, 15, 51

While it is admitted that excessive sedation may be deleterious in status asthmaticus, it is submitted that liminal sedation is often beneficial and will neither accelerate nor alleviate progressive bronchial occlusion.

Atkinson Morley's Hospital
Wimbledon, London, S W 20

BRYAN BROOM

THE PERSONAL DOCTOR

SIR,—Before this instructive correspondence closes I should like to ask Dr Fox how much his definition of a personal doctor differs from that which I was rash enough, three years ago, to suggest for a general practitioner "A doctor in direct touch with patients, who accepts continuing responsibility for providing or arranging their general medical care, which includes the prevention and treatment of any illness or injury affecting the mind or any part of the body"[1] Analysis of significant differences between the two definitions should help this discussion.

In our country the doctor we now recognise as a good general practitioner is part of a comprehensive medical service in which he plays an important role—bringing the resources of modern medicine to the homes and bedsides of his patients, supporting, comforting, and befriending them and their families in the same personal way he has done in the past, and advising and guiding them wisely when they need to seek specialist help

That general practice is evolving like this, fitting into the modern framework of medicine, is natural It is a challenge to us all to improve this branch of our profession in the ways which Dr Fox suggests, but *not* a reason for changing its name

London, S W 1

JOHN H HUNT

*** Dr Fox writes "My article was a plea for the preservation and strengthening of the independent practitioner as Dr Hunt describes him But I argued that his days are numbered unless he is seen to justify his independence Whether we give him a new name is unimportant, for names notoriously outlast functions But in judging his adequacy and survival-value we should apply, I suggested, a new criterion Is he giving better personal care than would be obtainable from a hospital group?"—ED L

PHOTOCOPYING

SIR,—I have read with interest the letter from Dr Graham in your issue of May 14, and I would subscribe fully to his condemnation of the use of trichlorethylene and of tricresyl phosphate when used in transparentising solutions for application to opaque originals which are to be reproduced by contact printing But I think Dr Graham has assumed the existence of a danger which does not exist or is very remote Over nearly forty years' connection with the photoprinting industry I have not known trichlorethylene or tricresyl phosphate to be used in transparentising fluids

Further, it should be borne in mind that transparentising is not a regular procedure in the photoprinting industry It is an application made when original drawings have become so old through age or handling that it is desirable to make them more transparent before copying, and as such the individual is exposed neither to the effects of a high toxic concentration of the vapours of the solvents used, nor to the long-continued in[illegible] of a low vapour concentration whereby a cumulative [illegible] effect is produced in the system

Another substance which Dr Graham mentions, namely carbon tetrachloride, although banned in industry except under controlled conditions of ventilation has for many years been freely sold for purposes of dry-cleaning in the household.

The point I would make is that the transparentising of prints is not an operation often encountered in the photoprinting industry, which is in no way dependent upon the general usage of the solvents to which Dr Graham quite rightly takes exception.

Loughton, Essex.

H D MURRAY
Director, Ozalid Company Limited

PERIORBITAL ŒDEMA AFTER EXERTION

SIR,—Sometimes the cases that Captain Mullan refers to (April 9) have predominant œdema of the conjunctiva and lids, the lids less frequently It is a white chemosis, which subsides spontaneously but more rapidly when a corticosteroid is applied locally

It may be due to an allergy to lactic acid Loose tissues such as the conjunctiva and lids seem to be extremely sensitive to lactic acid allergy We suggest hydrocortisone eye drops instilled before the exertion A skin-test may be able to confirm the diagnosis

Academisch Ziekenhuis,
Ghent, Belgium

ADOLPH NEETENS

METAHEXAMIDE IN THE TREATMENT OF DIABETES MELLITUS

SIR,—Metahexamide [1-(3-amino-*p*-tolylsulphonyl)-3-cyclohexylurea], a new oral hypoglycæmic agent, was recently introduced for the treatment of diabetes mellitus and has since been withdrawn owing to its toxic effects on the liver[1,2] Its half-life is 18 2 hours[3] as compared with 35 hours for chlorpropamide, 40 hours for carbutamide and 3 5 hours for tolbutamide.[4]

The drug was given to 27 diabetic patients as a single daily dose before breakfast, 300 mg on the first day, 200 mg on the second day, and 100 mg on subsequent days All patients were treated for at least seven days before the compound was considered to have failed to control their diabetes A patient was considered to be well controlled on metahexamide when the morning specimen of urine was sugar free and a blood sugar at least $1\frac{1}{2}$ hours after breakfast below 210 mg per 100 ml

The first group of 16 patients consisted of 9 who had failed to respond to tolbutamide, 1 who had failed to respond to chlorpropamide, and 6 who had failed on both tolbutamide and chlorpropamide, on separate occasions None of these 16 cases responded to metahexamide All were the type of case which would be expected to respond to oral hypoglycæmic agents[5,6] A further 11 cases were changed from good control on tolbutamide, chlorpropamide, or insulin, and 9 of these showed good control on metahexamide Of the 2 cases which failed, 1 had previously been well controlled on chlorpropamide and the other was an obese diabetic who has since been shown to be unresponsive to other oral hypoglycæmic agents

The weight remained unchanged in 14 of the 27 cases treated, 8 patients lost weight and in 6 cases there was a relapse in the diabetic control 5 patients gained weight and of these only 2 showed a satisfactory response to metahexamide No toxic effects were recorded in any patient in our series

There is sufficient evidence in this small series to show that metahexamide has no advantage over tolbutamide and also has a smaller range of activity than chlorpropamide[7] The trial was stopped at this stage following a report that metahexamide had produced necrosis of the liver in 1 case There would therefore seem to be no indication for the use of metahexamide in the treatment of diabetes, and it has now been withdrawn by the manufacturers

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[1] *Brit med J* 1957, i, 1075

[1] Owen, J A *Metabolism*, 1959 8, 667
[2] Mach, B, Field R A, Taft, E B *New Engl J Med* 1959, 261 438
[3] Morgenstern, L L, Garrett, E R *Ann N Y Acad Sci* 1959, 82, [illegible]
[4] Stowers, J M, Constable, L W, Hunter, R B 1959, [illegible] 74 689
[5] Nabarro, J D H *Brit med J* 1959, i, 1466
[6] Oakley, W G *Practitioner*, 1959, 183, 478
[7] Jackson, D, Oakley, W G *Lancet*, 1959, ii, 752

Diabetic Clinic, King's College Hospital, London, S.E.5

DERRICK JACKSON
WILFRID OAKLEY

SALMONELLA OSTEITIS

SIR,—Dr Reid's comments (April 9) on the possible ætiological role of *Salmonella enteritidis* var *chaco* in some of our cases of salmonella osteitis[1] were much appreciated We must point out however that none of our cases in which *S enteritidis* was isolated resembled the syndrome described by Cosgrove and Reid,[2] nor was the clinical picture presented by these cases essentially different from that presented by cases in which other strains of salmonellæ were isolated In all our patients pain and swelling over the affected bones were *presenting* symptoms, and not sequels to a typhoid-like illness Finally, it was confirmed bacteriologically that we were dealing with *S enteritidis* var *jena*

Children s Department and Department of Bacteriology, University College Hospital, Ibadan, Nigeria

R G HENDRICKSE
PATRICK COLLARD

POSTURAL TREATMENT OF ADHESIVE OBSTRUCTION OF BOWEL

SIR,—Since decompression via an intestinal tube can at times relieve this form of obstruction it is plain that in such instances there is no permanent stricture If instead a laparotomy is done one can sometimes lift the laden bowel on the proximal side of the kink into alignment with that on the distal side It should be possible to use gravity for this unkinking, and in selected patients posturing has been found effective On such occasions the patient is spared the discomfort of intestinal tube and operation

Postures used—The history may indicate a posture If not I use the following sequence With the foot of the bed elevated on 18-in blocks, the patient lies (i) on his right then (ii) on his left side and then (iii) prone. Twenty minutes are spent in each position If all fail the patient is put in (iv) the upside down position Here he takes his weight on his shoulders, the trunk and lower limbs resting against the wall

It is appreciated that the diagnosis is not fully confirmed unless the adhesion is seen at operation and that the examples which follow are open to objection on this score but one object of the method is to prevent operation.

(1) In October, 1954, Mrs A had an operation for bilateral pyosalpinx. Nine days later, a gynæcologist, Mr. H R Thomson, and I operated for intestinal obstruction Several inches of small bowel were densely adherent to the pelvic floor In March, 1955, she was readmitted with a second obstruction and treated by intestinal tube and intravenous fluid On Oct. 31, 1955, the patient had an exactly similar midline hypogastric colic. Two minutes after being placed upside down she felt a gurgling and had immediate relief

(2) Mr B was admitted to Launceston General Hospital in 1955 after thirty-six hours of upper median abdominal colic and two vomits In 1940 he had an appendicectomy, and in 1947, 1951, and 1954 laparotomies to divide adhesions At the 1955 admission postural treatment was given With the foot of the bed raised, the right lateral position was soon followed by passage of wind per rectum and relief of pain

(3) Mrs C was admitted to Launceston General Hospital in August, 1958, with a five-hour history of hypogastric colic and six vomits She had an appendicectomy in 1942 and pelvic cellulitis in 1946 Radiography of the supine abdomen showed two gas-filled coils of small bowel and, in the erect position, fluid levels Postural treatment was given and in the first three positions the patient vomited Her body was then supported against the wall while she took her weight on her shoulders Soon she felt a rumble which ended in the passage of flatus and relief of pain

Selection and safeguards—(1) Posturing should never be attempted if (*a*) a closed loop of small bowel or (*b*) a large bowel obstruction is likely, the latter because the ileocæcal valve may remain competent thus virtually converting the obstructed colon into a closed loop (2) Temporary disimpaction of a mobile object at a neoplasm might conceivably follow posturing Accordingly at times I have sought tumours after postural treatment, so far with no result (3) In a patient referred by Dr R A Godfrey-Smith posturing failed Intubation then also failed Operation revealed a hard band causing pressure necrosis of bowel wall This illustrates the well-known need for very early operation if conservative measures fail Provided this danger is remembered I believe that posturing will upon occasion obviate intestinal tube and/or operation in adhesive obstruction

I have not seen this idea in print it is the result of a question put in 1950 by Mr C Craig On dividing a fibrotic and obviously matured adhesion he asked how it was that the patient had avoided intestinal obstruction for so long

Launceston, Tasmania

W W WOODWARD

EXPIRED-AIR RESUSCITATION

SIR,—Dr Gardner (May 7) mentions that it is no great hazard if air is blown into the stomach Though the most important thing, of course, is that oxygen quickly reaches the patient's lung, blowing air into the stomach during inflation of the lung is most undesirable not so much because it may impair diaphragmatic movement, but because it may provoke dangerous regurgitation It is often reported that the use of expired-air insufflation resulted in water and stomach contents being forcefully expelled from the victim Sometimes stomach contents have been blown into the deeper airways of the patient, thereby jeopardising what seemed to be an otherwise successful resuscitation It may also be unwise, therefore, to express air from the stomach, for this may result in stomach contents being expelled too

Probably when the air-passage is clear and the inflation pressure is limited to 20 cm water, then air is rarely blown into the stomach But it is hardly possible to teach this, and even more to have a "frightened" lay rescuer remember limiting inflation pressure A practical possibility, however, seems to be inflation through the nose rather than the mouth In studies[1] with more than 1000 anæsthetised, curarised, and non-relaxed patients, it was found that inflation through the nose seldom resulted in only stomach inflation, possibly because this route with its increased resistance cuts down the peak pressure reaching the pharynx. Incidentally, not a single case of nasal obstruction was observed during this study

That practice manikins "form an integral part in any comprehensive training scheme" seems true[2,3] However, it must be presumed that, apart from being suitable for the actual training technique, the manikin is not by itself a source of spread of infection It would be silly to have hygienic objections with expired-air resuscitation in an emergency and not safeguard against cross-infection during training Not only the exterior of the manikin's face must be capable of disinfection, but also its air-passages, including its lung (and stomach)

Dr Gardner says "the impossible—practice manikins—

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[1] Hendrickse R G Collard, P *Lancet*, Jan 9 1960 p 80
[2] Cosgrove, P C, Reid, J D *Trans R Soc trop Med Hyg* 1955, 47, 153

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[1] Elam, J O, Greene, D G Schneider M A, Ruben H M Gordon A S Hustead, R F, Benson, D W, Clements J A *J Amer med Ass* 1960, 172, 812
[2] Ruben, A, Elam J O, Ruben, H *Lancet*, 1959 ii 69
[3] Ruben H, Ruben A Elam J O, Benveniste D *Ugeskr Læg* 1960, 122, 215

will take a little longer." A practice manikin is now constructed to fulfil not only the technical demands (inflation through nose or mouth, mimicking air-passage obstruction and its release, stomach inflation when improper inflation pressure is used), but also allowing proper hygienic precautions to be taken[4], and such a manikin is available in Denmark (Testa Laboratorium, Copenhagen).

Department of Anæsthesia,
The Finsen Institute, Copenhagen

HENNING RUBEN
Director

SIR,—There are a number of points on which I should like to comment. First, patients whose breathing has stopped or is failing may be classified into three groups:

(*a*) Those who will recover with or without treatment.
(*b*) Those who require assistance in respiration in order to survive.
(*c*) Those who are beyond aid.

Artificial respiration is taught for the benefit of the second group, but since this is not homogeneous the extent of the help which is needed will vary from complete dependence on the method employed to a short application of such a manœuvre. Testing these procedures is therefore difficult in the "field", and for a realistic assessment the measurement of tidal volumes and oxygen uptakes on paralysed but otherwise normal subjects must be used instead. In this way a number of important factors are ignored, such as the effect on the cardiovascular system, but such an appraisal does give the Holger-Nielsen method a good deal of support in preference to other manual procedures[5]. Further, it is effective in patients whose lungs are resistant to deformation, as in emphysema, and this may be of importance under the conditions where artificial respiration may have to be employed.

On the other hand, expired-air resuscitation seems to have had little testing on the edentulous subject and in patients with a decreased lung compliance (as in emphysema), both of which would place the operator and the patient at a disadvantage. The fact that an airway may not always be available is an argument against the procedure, as is the need for apparatus in Eve's method. In addition, the anæsthetist is not the man who is going to do artificial respiration in most cases out of hospital. The layman who is going to carry it out must be trained and the technique which he is taught must be effective, simple, and in no circumstances harmful.

The "mouth-to-mouth" technique is difficult to perform efficiently and at present its value is unproven in conditions other than the ideal. But reports on the Holger-Nielsen procedure[6 7] led the medical advisers of the St. John Ambulance Association, the British Red Cross Society, and the Royal Humane Society, amongst others, to recommend its adoption. Surely it is unwise to change the standard teaching until the evidence is more conclusive.

University of Bristol

R. ST. J. BUXTON

TREATMENT OF DEAF CHILDREN

SIR,—A number of our profession have been approached by medical practitioners concerning the rehabilitation of children suffering from adventitious deafness. We should be grateful if, through your columns, we might stress the urgency of such treatment to conserve their communication skills, which, without immediate treatment, are speedily lost.

This society will be glad to supply the names of qualified specialist teachers of the deaf who could be called upon to deal with this problem in any given locality.

2, Newcourt Road,
Charlton Kings,
Cheltenham, Glos.

J. DIMOND-HOGG
Honorary secretary,
Society of Teachers of the Deaf

NON-STERILE INJECTIONS?

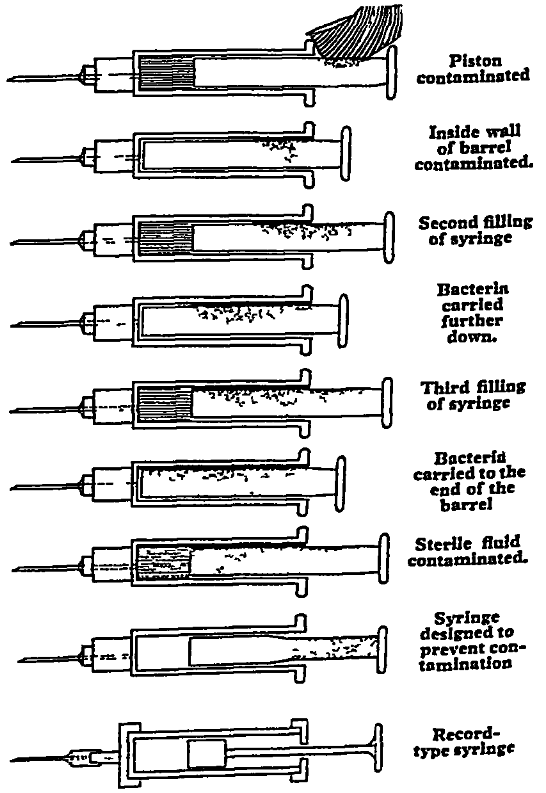
SIR,—I believe that it is not generally appreciated that contamination of an injection fluid by other than blood-borne organisms can occur, when using a single all-glass syringe for a series of immunising injections, unless strict attention is paid to the method of manipulation.

A commonly used technique seems to be to hold the ampoule, or the multiple-dose bottle, in one hand, placing the index finger of the other hand on the end of the barrel of the syringe, and in contact with the shaft of the piston (see figure), and exerting traction with the middle finger and the thumb. While this is a perfectly suitable technique for a single injection with an all-glass syringe, or even for a series of injections with a Record-type syringe, it should never be used for a series of injections with an all-glass syringe. The bacteria which are deposited on the piston by the finger are carried down during injection of the fluid, to come into contact with the inside wall of the barrel of the syringe. With the next filling of the syringe, the sterile fluid washes the contaminated inside wall of the barrel.

It might appear, at first, that this contamination cannot occur when only small volumes of fluid are taken into the syringe, and the piston is not withdrawn to its fullest extent, but a few moments' reflection will reveal the fact that contamination by the fingers of the proximal end of the shaft of the piston, will result in contamination of the whole of the inside wall of the body of the syringe after two or three repeated withdrawals and ejections—the bacteria are carried further down inside the syringe with each successive movement of the piston (see figure). It is even possible that the process may be hastened by currents set up as a result of pressure changes within the syringe.

Contamination of a sterile fluid within the syringe itself can occur, in a like manner, if the above technique is used for withdrawing the piston of an all-glass syringe before the introduction of air into a multiple-dose bottle. It may well be that the sterile fluid comes into contact with the contaminated inside wall of the syringe with the very first filling.

In order to avoid contamination of the piston of an all-glass syringe, a technique must be practised whereby the ampoule, or the bottle, and the barrel of the syringe are both held in the


Piston contaminated
Inside wall of barrel contaminated.
Second filling of syringe
Bacteria carried further down.
Third filling of syringe
Bacteria carried to the end of the barrel
Sterile fluid contaminated.
Syringe designed to prevent contamination
Record-type syringe

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4. Ruben, H. *Brit. med. J.* (in the press).
5. Buxton, R. St. J., Kazantzis, G. *Med. Pr.* 1956, 236, 611.
6. Holstein-Rathlou, E. von. The Holger-Nielsen methods: history and scientific basis. Copenhagen, 1950.
7. Gordon, A. S., Affeldt, J. E., Sadove, M., Raymon, F., Whittenberger, J. L., Ivy, A. C. *J. appl. Physiol.* 1951, 4, 408.

fingers of one hand, leaving the other hand free to pull on the piston by touching the "handle" part only. Even then, with the piston fully withdrawn, strict vigilance is necessary during subsequent manipulation, in order to avoid touching the exposed shaft with the fingers or with the palm of the hand.

The provision of a freshly sterilised syringe and needle for each injection at immunisation clinics must surely be the safest and most sensible technique to adopt. However, when circumstances are such that one syringe only is to be used for a series of immunising injections, I would suggest that the Record-type syringe should be the syringe of choice. Contamination of the piston of the Record syringe by the fingers or by the hand cannot occur, and no special technique or vigilance is necessary (see figure).

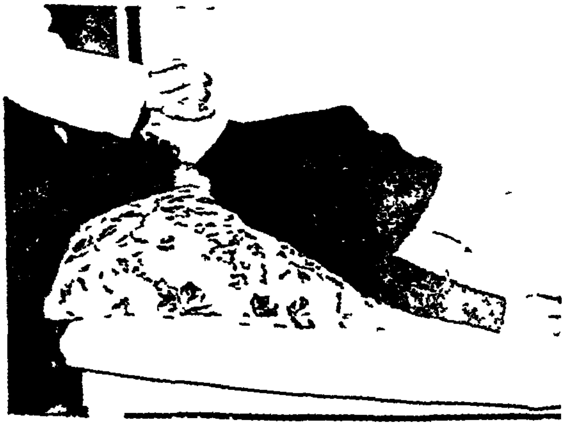
For those who prefer an all-glass syringe on all occasions, possibly the manufacturers would be able to produce a syringe with a piston so designed that it made contact with the inside wall of the barrel for a part of its length only, the rest of the glass shaft being of slightly smaller diameter (see figure). The use of such a syringe would eliminate, in a like manner, any possibility of accidental contamination of the piston and of the syringe contents.

Nelson,
New Zealand. JOHN MEAD.

A PILLOW FOR USE IN CERVICAL MANIPULATION

SIR,—When working single-handed in general practice one often has difficulty in applying counter-traction during manipulations of the neck. In order to obviate this a pillow has been designed and its method of use is illustrated below.

The pillow is triangular in cross-section, being approximately 7 in. from base to apex and 20 in. each way at the base. I use a couch 6 ft. 6 in. long, 20 in. wide, and 20 in. high for manipulations (the same couch can be used for ordinary examinations). The pillow is placed at the end of the couch (see figure) and the patient's shoulders are brought up to the apex, thus leaving the neck freely mobile in all directions.



The advantages of this pillow are:

(*a*) The patient's weight provides the counter-traction.

(*b*) The angle of pull is a "natural" one, thus avoiding strain on the back of the operator.

(*c*) The build of the patient governs the amount of traction applicable, relating it to the conformation of the neck.

(*d*) It is inexpensive.

Hillcrest, Natal. PHILIP H. DALGLEISH.

ERYTHROCYTE ENZYME DEFICIENCY IN UNEXPLAINED KERNICTERUS

SIR,—Kernicterus in full-term infants in Singapore is not uncommon. The pædiatric unit of the General Hospital admits approximately 40 infants per annum in whom the central-nervous-system damage is already present, and some other cases with a high serum-bilirubin requiring exchange transfusion. The majority of these cases are not due to blood-group incompatibility.[1 2] In some cases there is a family history of severe neonatal jaundice which has been fatal or has left residual central-nervous-system damage.

The mother of such a family in which 3 infants were so affected has been investigated for a hæmolytic anæmia which was found to be associated with deficiency of glucose-6-phosphate-dehydrogenase in her erythrocytes.[3] In this lady the precipitating agent was either pyridium or sulphamethoxypyridazine, but many other substances have been reported as causing this syndrome (primaquine, sulphanilamide, acetanilide, phenylhydrazine, sulphoxone, phenacetin, acetylsulphanilamide, sulphacetamide, thiazolsulphone). The same enzyme deficiency is found in favism.[4] This family had previously been investigated by us but no enzyme studies were performed and no explanation was found for the severe jaundice in the affected infants.

The blood of full-term infants with clinical features similar to those of the affected infants in the above family have been examined for glucose-6-phosphate-dehydrogenase activity by a simple colorimetric method devised by Motulsky and Campbell (see Vella[5]). Blood-group incompatibility was excluded in all cases. All infants were seen and examined clinically during the acute episode of jaundice by one of us. The clinical diagnosis of kernicterus was confirmed by necropsy in those children who died and by neurological sequelæ in those who survived the neonatal period. The results in 14 cases show that enzyme activity was absent or deficient in 13.

Case no.	*Ethnic group*	*Sex*	*Glucose-6-phosphate-dehydrogenase*
1	Chinese	Female	Absent
2	Chinese	Female	Absent
3	Chinese	Male	Absent
4	Chinese	Male	Absent
5	Chinese	Male	Absent
6	Chinese	Male	Absent
7	Chinese	Male	Absent
8	Chinese	Male	Absent
9	Chinese	Female	Intermediate
10	Chinese	Female	Absent
11	Chinese	Female	Absent
12	Chinese	Female	Absent
13	Malay	Male	Absent
14	Chinese	Female	Present

Enzyme activity was *absent* when decolorisation did not occur, in duplicate estimations, before 100 minutes. It was *present* when decolorisation occurred between 30 and 70 minutes, and *intermediate* when decolorisation occurred repeatedly at about 100 minutes.

Case 3 was interesting because this infant was one of male twins with dissimilar blood-groups. He died 2 days after admission, aged 8 days, and the diagnosis of kernicterus was confirmed at necropsy. His brother was healthy with only slight jaundice and normal enzyme activity and has progressed normally. It is probable that this syndrome of unexplained severe neonatal jaundice causing kernicterus is in many cases the result of sudden hæmolysis in infants whose erythrocytes have this inherited abnormality. The factor (or factors) precipitating hæmolysis is at present unknown. Hæmatological observations and results of an investigation to determine the responsible agent in these infants will be published later.

The kernicterus syndrome in Singapore occurs predominantly amongst Chinese infants. One of us has examined cord-blood samples from infants born in Singapore and found an incidence of glucose-6-phosphate-dehydrogenase deficiency in 2 (2·6%) out of 76 specimens from Chinese males. A

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1. Maycock, H. G. T., Gibson-Hill, M. M. H. *Med. J. Malaya*, 1954, 8, 343.
2. Wong, H. B. *Arch. Dis. Childh.* 1957, 32, 85.
3. Vella, F., Phoon, W. O. *Med. J. Malaya* 1959, 13, 300.
4. Beutler, E. *Blood* 1959, 14, 103.
5. Vella, F. *ibid.* p. 295.

deficiency was also found in 3 (4 7%) out of 63 male adult Indians It is therefore probable that the factor precipitating hæmolysis is related to traditional Chinese methods of caring for the mother and baby during the puerperium

This syndrome undoubtedly belongs to the group of enzyme-deficiency hæmolytic anæmias discussed by Lanzza et al (March 12) In our infants the presenting symptom is severe jaundice which often kills before the hæmoglobin falls very low This is presumably due to the immature liver function during the first week of life

We are grateful to the Director of Medical Services in Singapore for permission to publish this report

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F VELLA

SERUM THROMBOCYTOPOIETIC ACTIVITY IN IDIOPATHIC THROMBOCYTOPENIC PURPURA

SIR,—We reported earlier that the serum of thrombocythæmic[1] and some thrombocytopenic[2] patients contained a factor, called thrombopoietin, capable of inducing a significant thrombocytosis of several days' duration in mice

This factor is retained by a dialysing membrane, is destroyed by trypsin, runs with the β-globulins in electrophoresis, and is counteracted by normal human serum in the mouse[1 2] We concluded that the biological assay used in our experiments indicated the equilibrium between the thrombopoietic factor and its biological inhibitor(s), and that this equilibrium was much disturbed in some pathological conditions

After these observations, sera from 20 thrombocytopenic patients were tested, each on two occasions, except in a patient with hæmoblastosis and another with symptoms of hypersplenism

0 2 ml of fresh serum was given intravenously to 4–6 mice Direct platelet-counts were made by phase-contrast microscopy before and 48 hours after the injection When the platelet-count increased by more than an average of 30% the result was denoted as positive, and changes of less than 30% were negative

Results are as follows

	Positive	*Negative*
Cases with hypoplastic or aplastic megakaryocytopoiesis		
Hæmoblastosis	2	3
Carcinomatosis	1	
Idiopathic panmyelopathy	1	2
Cases with hyperplastic megakaryocytopoiesis		
Acute idiopathic thrombocytopenic purpura	3	
Chronic idiopathic thrombocytopenic purpura	1	4
Cirrhosis of the liver with hypersplenism	3	

The serum of subjects with physiological thrombocytopoiesis is "negative"

Although the results of individual cases were reproducible, it seems that the thrombocytopoietic activity was variable even under seemingly similar conditions However, serum samples from patients with *untreated acute* idiopathic thrombocytopenic purpura (I T P) showed *enhanced* activity The defect in acute I T P is, therefore, something other than thrombopoietin deficiency This enhanced activity was, however, no longer demonstrable in our 2 cases in which thrombopoietic activity was determined 36–48 hours after starting prednisone therapy (75–100 mg per day)

Briggs and Verstraete[3] lately tabulated some differences between acute and chronic I T P Unlike sera in acute I T P , sera from chronic I T P cases, with 1 exception, did not show demonstrable thrombocytopoietic activity

In agreement with these results, Schulman et al[4] have recently noted that in a case of plasma-factor dependent chronic I T P the plasma of an acute I T P patient was able to elicit thrombocytosis On the other hand, even repeated infusions of plasma from a patient with essential thrombocytosis failed to induce remission in a case of acute I T P (Cochrane, see discussion to Schulman et al[4])

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PREDICTION OF OPERATIVE BLEEDING IN HÆMOPHILIA

SIR,—Owing to the difficulty in measuring the exact level of antihæmophilic globulin in hæmophilic blood,[5] elective surgery in these patients is liable to be hazardous

The simple method (which can be carried out within half an hour of obtaining a blood sample) described in the accompanying table, which gives the final balance between the activity of antihæmophilic globulin and that of Bridge anticoagulant,[6] was thought to provide a good index to changes in the pathological defect Accordingly, it was used on five occasions in order to test its suitability in indicating the safety of operative procedure after antihæmophilic-globulin therapy The substrate clotting-times obtained and the amounts of bleeding recorded are shown in the table

RELATION BETWEEN THE SUBSTRATE CLOTTING-TIME AND OPERATIVE BLEEDING

Patient	Operation	Substrate clotting-time*	Bleeding
A	1 Ureter transplantation	20	Controllable
	2 Ectopic bladder excision	63	Excessive
B	Tracheostomy	12	Normal
C	Cataract	$11^1/_2$	Normal
D	Tonsillectomy	16	Normal

* Blood sample, *obtained immediately before the operation from a vein* other than that used for the administration of A H G , was tested by a person who had no previous knowledge of the amount of A H G injected The plasma, after being tested with $Al(OH)_3$ suspension, was incubated *undiluted* with equal volumes of normal serum (1 10), platelet suspension, imidazole buffer pH 7 3, and 0 05 *M* $CaCl_2$ After 6 minutes, 0 1 ml of the mixture, together with 0 1 ml 0 025 *M* $CaCl_2$, was added to 0 1 ml substrate (*patient s* plasma), recording the clotting time

From these results, it is now reasonable to recommend that this simple test should be utilised in controlling and timing surgery, if the clotting-time of a preoperative blood specimen is found to be less than 20 seconds, surgery can be proceeded with, but if the time exceeds 20 seconds further antihæmophilic globulin must be resorted to before doing so

Blood Transfusion Centre,
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F NOUR-ELDIN

"PSYCHOLOGICAL OVERLAY"

SIR,—May I be allowed to make a plea—not on behalf of my fellow nurses, but for our patients?

It is becoming increasingly common these days to state on a patient's notes—usually after many months of treatment—that there is a "large psychological overlay" Perhaps the doctors are sometimes right—and I have particularly in mind the prevalent "slipped disc"—but if you were strictly honest you should more often admit that either your diagnosis was wrong or your treatment was a failure

A "psychological overlay" is a very convenient umbrella under which to shelter, but from the patient's angle it is a complete write-off From now on he is a neurotic, the trouble is with himself The pain exists not in his back but *in his mind*, and he is a waster of precious time, for until he decides for himself that he is going to get better there is nothing else to be done

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[1] Kelemen, E., Cserhati I Tanos B *Acta hæmatol , Basel*, 1958, 20, 350
[2] Rák, K. Cserháti, I , Kelemen E *Med Exp , Basel*, 1959 1, 125
[3] Briggs, D K Verstraete, M International Textbook of Allergy, p 544 Oxford, 1959
[4] Schulman I , Pierce, M , Lukens, A , Currimbhoy, Z , Fort, E *Amer J Dis Child* 1959, 98 633
[5] Nour-Eldin, F 7th European Congress of Hæmatology, London, September, 1959
[6] Nour-Eldin, F , Wilkinson, J F *Brit J Hæmatol* 1958, 4, 38, 292

If after all the doctor's skill and care the patient is nothing bettered but rather made worse, could doctors not be more honest about it? Would they care to be known as "psychologically overlaid"? I know I wouldn't.

Slough MARY KAY

BLOOD-GROUPS AND DISEASE

SIR,—I should like to draw attention to certain points which may be of importance in evaluating the results of studies on the distribution of blood-groups in different diseases

(1) *Absence of a basic idea*.—Investigations on the distribution of the blood-groups are generally performed without a working hypothesis The frequencies obtained are then compared with those of a control material or an entire population. The significance of the differences, moreover, is calculated by various statistical methods

"Statistically significant" differences in these circumstances are affected by the number of factors considered in the investigation. In blood-group studies the material is divided into at least four (often eight or more) parts, depending on the number of blood-group factors observed. The material can be divided still further by the patients' age, year of birth, sex, or any other easily recognisable attribute The number of the combinations can rise to the hundreds, but generally only a part of them are reported.

It is only to be expected, then, that "statistically significant" differences will be established in nearly every material It is naturally impossible to predict the combinations in which the differences will occur, nor can these differences usually be established in other authors' materials

This has happened, for example, in the investigation by Yates and Pearce[1] in which it was found that the blood-group distribution of astrocytomas changed after 1945 At first the authors failed to find any major differences from the control material Small manipulation however, brought out a significant difference in the O group when the material was divided (obviously independently of the patient's age) by the year of examination

This is the procedure often applied in clinical-statistical studies Provided there are sufficient factors to be examined, the result is that differences and coincidences are almost always encountered. Clinical experience and common-sense, however, usually reveal the real reason for these differences and obviate the need for mathematical study There is no sentiment involved in the study of blood-groups, and little experience to draw on. It is hardly surprising, then, that common sense is often forgotten in analysing the results

An unexpected distribution of blood-groups is in fact comparable with the way the cards fall when dealt For a player to get a hand of 13 spades is rare but not impossible The dealer cannot be blamed (though he might be suspected), but the result, statistically confirmed is not published in a bridge magazine

(2) *Selective factors*.—One selective factor was discussed above the material is divided up in order to make the differences emerge Mention is omitted of previous unsuccessful attempts in dividing up the material

It must also be regarded as probable that the authors have at their disposal several sets of material and concentrate on those which show up the differences most distinctly

Finally, it is certain that the materials in which differences are shown tend to appear in print more readily than those in which no differences are found This may lead to a flow of reports resulting finally in the conclusion that the differences observed are correct Indeed, the publication of another study indicating differences in agreement with the study published is more likely than a new report finding no differences Courtesy alone may prevent the publication of the latter When somebody ultimately collects all the materials reported in the world literature, the point is established Q E D

In general scientific research without a working hypothesis and basic idea will hardly ever produce results, whatever it may appear to do at first glance. This is likely to be true also of blood-group research

Finnish Red Cross Blood Transfusion
Service, Helsinki
H R. NEVANLINNA.

Parliament

QUESTION TIME

Children and the Courts

IN answer to a question Mr DENNIS VOSPER, an under-secretary of State to the Home Office, said that between Jan 1, 1950, and Dec. 31, 1959, 32,550 children were brought before juvenile courts in England and Wales as being in need of care or protection and were dealt with in the following ways

Ordered to be sent to an approved school	2385
Committed to the care of a fit person	13,577
Parent ordered to enter into a recognisance to exercise proper care and guardianship	683
Supervision order alone	11,542
No order made	4363

Mr ALAN BROWN Is the Minister aware that Britain is now among the minority of countries in which child victims of lack of protection or of cruelty or neglect can still be brought before courts of summary criminal jurisdiction? Would he consider setting up courts of guardianship before which this class of children could be brought? Mr VOSPER The Ingleby Committee is shortly to report. It is considering the whole question and I would rather not make a further comment at this stage

Miss ALICE BACON Is the Minister aware that magistrates in juvenile courts find themselves in an extremely difficult position because they have nowhere to send juvenile offenders on remand? Is he aware that recently a magistrate said that he never slept at night after he had been working at the juvenile court? Does not the Minister agree that even before the Ingleby Committee reports one of the most urgent things to be considered is the provision of more remand homes?—Mr VOSPER A Bill is before the House dealing in detail with this subject. The Home Secretary is giving consideration to that aspect of the matter in advance of the Ingleby Committee recommendations

Mr SYDNEY SILVERMAN Should not the right hon Gentleman also be asked to consider whether the juvenile courts are in any difficulty at all? In the case of very young people, juvenile persons who are not yet convicted and are on remand if there is any real difficulty in finding a suitable place for them to go, is it not infinitely better to send them home than to send them to jail?—Mr VOSPER In general there is no difficulty in finding a place in a remand home The difficulty arises with those people who are so unruly that the remand home itself is not suitable.

Consultants' Letters

Mr W GRIFFITHS asked the Minister of Health whether he was aware that the National Health Service patients of some general medical practitioners in Manchester, having been referred to certain consultants, were not seen by these consultants but by a registrar, and what steps were taken to ensure that all consultants attended regularly and promptly the sessions at the hospital in accordance with their contracts —Miss PITT replied If the hon Member will give me details of what he has in mind, I will have inquiries made Mr GRIFFITHS Is the hon Lady aware that these complaints originate not from me but from members of the medical profession in Manches [illegible] from patients? Is she furth aware that I sent her department copies of specific allegations made by a general practitioner—a family doctor—who said

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[1] *Lancet*, 1960, i, 194

> " I am sick and tired of getting hospital reports back signed by the hospital registrar *p p* the consultant It is not the registrar's opinion I want, it is the consultant's "

These are the sort of complaints we are getting, reinforced by many letters from patients who, after attending a number of times at the outpatients' department, suddenly discover, sometimes by accident, that they are being seen not by the consultant they imagined they were seeing but by the registrar —and sometimes even by a house-man —MISS PITT I have seen a newspaper cutting which contains that statement, but I do not think I have seen any official letter from the hon Member with details amplifying such a statement. If he has such details, I shall be glad to look into them In any case, it is for the consultant to arrange how his own clinic should be held

Dr EDITH SUMMERSKILL In the event of a consultant not attending a clinic, is a deduction made in his remuneration ?—*MISS PITT Not to my knowledge, but I should like notice of that question*

Pay of Midwives

Dr SUMMERSKILL asked the Minister whether he was aware that domiciliary midwives were on call 123 hours a week for a weekly salary of £12, and whether he would take immediate action to improve these conditions —Mr WALKER-SMITH replied Pay and conditions of service of midwives are matters in the first instance for the Nurses and Midwives Whitley Council

Poliomyelitis in the Vaccinated

In answer to a question, Mr DEREK WALKER-SMITH, the Minister of Health, gave the following figures for cases of poliomyelitis in 1958 and 1959

Year	Group	Paralytic		Non-paralytic		Totals
		<15 yr	15 yr and over	<15 yr	15 yr and over	
1958	All cases	959	458	428	147	1992
	No among vaccinated†	88	4	83	3	178
1959*	All cases	512	220	215	74	1021
	No among vaccinated†	76	10	56	14	156

* Provisional figures
† Two or more injections of poliomyelitis vaccine

Expenditure on Social Services

The total current and capital expenditure on social services in the United Kingdom in 1959–60 was £3720 6 million (£1455 1 million from the Central Government, £1029 6 million from National Insurance Funds, and £1420 7 million from local authorities) Current and capital expenditure by all public authorities on the social services expressed as a percentage of the national income was 17 75% in 1951 and 19 5% in 1959

N H S Prescriptions

The average cost of prescriptions provided under the National Health Service in February, 1960, was approximately 6*s* 11*d*

Local Authorities' Mental Health Services

Of 146 authorities 120 have submitted to the Minister of Health their formal proposals for the development of community mental health services, and 14 have done so informally

Senior Registrars

On July 1, 1959, there were 120 registrars who had completed their training, of whom 78 were in their sixth or later year

Shortage of Dietitians

On Aug 1, 1959, 110 posts for therapeutic dietitians in the National Health Service were unfilled

Obituary

CONRAD MEREDYTH HINDS HOWELL

M A, D M Oxon, F R C P

Dr C M Hinds Howell, consulting physician to St Bartholomew's Hospital and to The National Hospital, Queen Square, died on May 9, at the age of 83

The son of Conrad Goodriche Howell, a barrister-at-law and an official of the Ecclesiastical Commission, he was educated at Marlborough, Trinity College, Oxford, and St Bartholomew's Hospital At Oxford he received a first-class in the honour school of natural science (physiology), and he entered Barts as a senior entrance scholar There he won the Kirkes scholarship and gold medal and the Brackenbury and Lawrence scholarships before qualifying in 1902 After holding junior appointments at Barts and at Queen Square, he was appointed to the staff of the Great Northern (later Royal Northern) Hospital in 1908 and The National Hospital in 1912 He was elected F R C P in 1912 In 1920 he became assistant physician at Barts and soon afterwards he resigned his appointment at the Royal Northern He was promoted physician to Barts, and retired from the active staff in 1937 at the retiring age of 60 which was in force at that time During the war he returned to work in the Barts E M S sector hospital at St Albans He remained on the active staff at The National Hospital until 1942 and for some years he was dean of its postgraduate school

Dr Hinds Howell gave much to the Royal College of Physicians of London, where he held the offices of counsellor, censor, senior censor, and treasurer He was the college representative on the committee of management of the Conjoint Board for twelve years, and was chairman for four years He was an examiner for the universities of Oxford and London and for the Conjoint Board As president of the section of neurology of the Royal Society of Medicine in 1935 he gave an address on arachnoiditis He was a founder member of the Association of British Neurologists and in 1946 was president of the British branch of the International League against Epilepsy

J A T writes

" Dr Hinds Howell was primarily a neurologist but he was also a general physician of wide knowledge and experience, and he was a stimulating teacher with a pleasing wit He developed a remarkable facility for injecting the gasserian ganglion under general anæsthesia, a difficult procedure but one in which he rarely failed His kindness and sympathy to patients was an inspiration to a succession of his house-physicians During his late fifties and early sixties he had a number of illnesses, but he made an excellent recovery and during the last twenty years of his life he was full of vigour He was working till a week before his death

" As a young man he was a keen cricketer and he was a member of the M C C for sixty years He had been in the Marlborough first XI and for many years captained 'the Past in the annual Barts Past *v* Present cricket match Later on he became a keen fisherman and a good shot He was also interested in painting and philately "

A further tribute comes from G G

" Hinds Howell (Con to his friends) was an excellent teacher not only in neurology but also in medicine, as he taught the general principles in a way which made the students remember them and better able to appreciate details taught by the other physicians As neurology became more and more specialised he was persuaded to start a neurological consultative clinic at which he saw patients referred to him by his colleagues This experience convinced him of the desirability of having a neurologist on the staff when he retired, and he welcomed the appointment of Dr Denny-Brown

"He was good at all games and played golf in the annual Staff *v* Students match until the outbreak of the war"

Dr Hinds Howell married Mabel Gulland, an Edinburgh medical graduate, in 1905 She died in 1958, and he is survived by three sons, one of whom is Dr C A Hinds Howell

PHILIP ELLMAN

F R.C.P

Dr Ellman, who died on May 10, was consulting physician to the rheumatism unit of St Stephen's Hospital, Fulham, and consulting physician for diseases of the chest to the North-East Metropolitan Regional Hospital Board As his appointments show, he had two specialties, and he made substantial contributions to each

After qualifying from the Manchester medical school in 1923, he continued his studies abroad in Frankfort and in Lausanne, where he took the degree of M D and held a research scholarship in clinical medicine at the cantonal hospital On his return to this country he held clinical assistantships at the Brompton Hospital, the Royal Chest Hospital, and the National Heart Hospital in London. He was also for a time assistant medical officer at Colindale Hospital and the West Middlesex Hospital and physician to the East Ham and Battersea Chest Clinic.

His work as physician to the St John Clinic and Institute of Physical Medicine in Pimlico gave scope for his interest in the rheumatic diseases With Sir Leonard Hill, who was director of research at the institute, he edited a course of lectures given by the staff which was published under the title of *The Rheumatic Diseases* When the institute and clinic were demolished to make room for a new housing estate, he joined the rheumatic unit at St Stephen's Hospital F B, who was his colleague there, writes

"This was a special unit sponsored by Sir Frederick Menzies, then chief medical officer of the London County Council We believed it to be a pioneer scheme in which a special unit was built up in a general hospital, and in which, for the first time, medical specialists, medical auxiliaries, almoners, and patients worked together as a team Ellman started annual weekend courses for general practitioners and those working for high qualifications, and he continued until a month before he died to be their stimulator and integrator He loved his bedside teaching of the medical students who came to us from the Westminster Hospital

"It was he who, I believe, coined the term 'rheumatoid disease' He published papers on the 'rheumatoid lung' He would argue heatedly if anyone doubted his evidence—as I well remember from the occasion when I pointed out to a foreign visitor the interesting geographical distribution of this condition, so common on his side of the ward, so rare on mine Many years ago he recognised the importance of psychological factors in 'fibrositis' It might be said that he was more interested in nomenclature than in management, but he was a good physician, and his papers on Morquio-Brailsford s disease, arthromyodysplasia congenita, acromegaly, and Felty s syndrome have found a place in the reference libraries of the world

"At St Stephen's we will miss this lovable man—his zeal, his enthusiasm, his interest in teaching, and his capacity for filling his day so full that he really made us feel that he was justified in continually putting off until the morrow matters that we wanted to settle on the day"

In his other specialty he also won the respect and affection of his colleagues One of them, J R B, writes

"Not only did Ellman stimulate his associates to do original work, but also he wrote extensively himself He made notable contributions particularly where rheumatology and diseases of the chest meet. His description of the pulmonary manifestations of the diffuse collagen diseases added an important link in the chain of knowledge of pulmonary infiltrations His chest unit at Plaistow was a model of its type, and the remarkable variety of excellent clinical material there was evidence of the breadth of his interests, and of his enthusiasm for accurate and complete diagnosis"

Outside this country he was known to many as editor of the *British Journal of Diseases of the Chest* T H S writes

"This was a project to which he gave his whole-hearted attention, and the way in which he chose and selected his contributors was a testimony to his knowledge in this branch He will best be remembered by his energy and enthusiasm, which were so often a stimulus to others and gave a delightful turn to his character In his professional life I suppose the one thing he would have been proudest to be called is a good doctor, and this he certainly was"

Dr Ellman leaves a widow, a son, and a daughter

Appointments

BRIERLEY, J S W, M.B Leeds assistant M O.H and assistant school M O, Rotherham.

LINGWOOD, MURIEL M, M.B Durh., D C.H. assistant M O, Kingston upon Thames and Wimbledon areas, Surrey

McLEAN, CHRISTINA J, M.B Edin. assistant M O H and school M.O, Smethwick.

MATHESON, K W, M.B., B.SC. Edin., D C.H, D.P.H deputy M.O.H., Nottingham

PIPER, G W, M.B. Lond., D.P.H M O.H, Holborn London.

SCOTT, O L S M.B. Cantab M.R.C.P honorary dermatologist, French Hospital and Dispensary, London

SHARP, MARY K., M.R.C.S. assistant M.O and school M O, Morley division, Yorkshire

SMITH A H., M.B Durh. assistant M O, Kingston upon Thames and Wimbledon areas, Surrey

SPEIRS, N T, M.B, B.SC. Edin, D.M.R.D consultant radiologist, East Lothian group of hospitals

*TOWNSEND, MARY, M.B. Lond., M.R.C.P, D C.H senior M O in charge of maternity and child welfare and school M.O Dorset.

WATSON, J A G, M.B Lond, D.P.H. deputy M.O.H. and deputy principal school M.O, Oxfordshire.

Sheffield Regional Hospital Board

ESPIR, M L E., M.B. Cantab, M.R C.P part-time consultant neurologist, Leicester group of hospitals

HUGHES, HUGH, M.B Birm. senior casualty officer, Scunthorpe and District War Memorial Hospital

WARDLE, C J, M.B. Lond, D.P.M. consultant in children s psychiatry, North Lincolnshire

Western Regional Hospital Board, Scotland

COYLE, T C., M.B. Glasg assistant in laboratory medicine, area laboratory Dumfries and Galloway Royal Infirmary

HAMILTON, CHRISTINA M, M.B. Glasg, D.P.M. assistant psychiatrist, Eastern District Hospital Glasgow

MILLER J H., M.B Glasg, F.R.C.S.E consultant surgeon, Glasgow Royal Infirmary

STIRLING G S, M.B Aberd, D.P.M. consultant psychiatrist, Crichton Royal Mental Hospital, Dumfries

Colonial Appointments

ACANNE, JEAN, M.B N U.I house-officer, Trinidad

BRINKERT, H C., M.D Amsterdam M.O Nigeria Northern Region

CHIPPENDALE IAN, M.B Cantab M O Hong Kong

CORDICE G J M.B Aberd M O H. St. Vincent Windward Islands

DALTON N T M.B. M.O, Nigeria Northern Region

FORBES, G I, L.R.C.P.E. D T.M & H, D.P.H M O, Hong Kong

HAMILTON, D M B.M. Oxon F.R.C.S surgeon medical department, Aden

HARTHOORN, HELENA J M B Lond. D OBST M O, Uganda

HOLMES R. G, M.B Lond. M.O, Uganda

JOHNSTONE, GEORGE F.R.F P.S. surgical specialist Tanganyika.

McCLEERY, C. H M.B Lond M O, Tanganyika

MATHEWS T C. H, M.R C.S, D T.M. & H D.P.H senior M.O, Kenya.

RENTON R. L. M.B. Aberd M O, Nigeria Northern Region.

WEBB, R. A J, M.B Lond. M O.H. Barbados

* Amended notice

Notes and News

PHARMACEUTICAL INQUIRY

THE Minister of Health has announced that the Central Health Services Council has, at his suggestion, appointed a standing committee, under the chairmanship of Lord Cohen of Birkenhead, to advise on operational research in the pharmaceutical services Its terms of reference are

> " Having regard to the need to avoid unnecessary expenditure in the pharmaceutical services provided under Part IV of the National Health Service Act, 1946, to advise the Minister on (1) the operational research which should be undertaken in relation to those services, involving the collection of statistical, economic and socio-medical data, and on (2) the interpretation of such data "

The other members of the committee are

Mr E F Collingwood, chairman, Newcastle Regional Hospital Board, Sir Hugh Linstead, M P , secretary, Pharmaceutical Society of Great Britain, Dr A Talbot Rogers, member, General Medical Services Committee, Mr J C Hanbury, chairman, Allen & Hanburys, Ltd , Mr H Noble, secretary, National Pharmaceutical Union, Dr H C Faulkner, general practitioner, London, Dr J C H Bird, general practitioner, Usk, Dr B Abel-Smith, lecturer in social science, London School of Economics, Mr L C H Tippett, principal statistician, British Cotton Industry Research Association, Mr R Falk, managing director, Marketing Development Company, Mr M Perrin, member, Advisory Council on Management Efficiency, and Wellcome Foundation, Mr G McLachlan, secretary, Nuffield Provincial Hospitals Trust

WORLD HEALTH ASSEMBLY

Prof V M Zhdanov (U S S R), the chairman, opening the technical discussions of the thirteenth World Health Assembly, now being held in Geneva, suggested that eradication of poliomyelitis was a practical possibility In Russia, he said " We therefore await with impatience the results of the immense programme of immunisation against poliomyelitis in the course of which it is intended in six months or a year to administer the [live virus] vaccine to not less than 80 million persons If this experiment proves truly satisfactory, it will answer the question of whether it is possible to eradicate poliomyelitis, at any rate for practical purposes, by means of mass immunisation of the population "

At a plenary session the following six member States were elected to designate a person to serve on the Executive Board of W H O Ghana, Thailand, Jordan, Korea, United Kingdom, and Argentina The Assembly expressed its appreciation of the invitation extended by the Government of India to hold the fourteenth World Health Assembly in India in February, 1961 The Assembly decided to extend the use of the Russian language in some W H O publications

The Committee on Programme and Budget recommended the Assembly to adopt a working budget for 1961 of $18,975,354 —some 12% more than the effective working budget for 1960 Introducing the budget, Dr M G Candau, director-general of W H O , said that eradication of communicable disease still represented the largest single item (31%) in the Organisation's regular budget, but in the long run the Organisation's most important work was still education and training

HOSPITAL INPATIENT INQUIRY

THE first part of a new report on the Hospital Inpatient Inquiry has appeared [1] This series, designed to provide supplementary information on the types of patient and disease treated, is published jointly by the Ministry of Health and the General Register Office

Part I gives summaries for selected conditions for 1958 and certain figures for 1955-57, which will be amplified in part II The survey is based on a 10% sample of discharges (including deaths) from National Health Service hospitals In England and Wales in 1958 the total discharges amounted to 3½ million Although for many conditions the number of discharges has increased since 1955, this may be due not to increasing prevalence, but to other factors such as more widespread admission to hospital A table shows the period patients have to wait for admission to hospital for different conditions For neoplasms of the lung in males, for example, 52% of patients are admitted immediately and 91% within a month For tonsils and adenoids, however, only 3 2% are admitted immediately and 23% within a month, 21% have to wait over six months for admission There were 75 9 admissions for maternity care per 100 births The hospital-delivery-rate averaged 57 5% in England and Wales in 1958, the highest rate being recorded in Greater London (69 1%)

CERTIFICATION

THE report of the National Insurance Advisory Committee [1] reaffirms the principles of certification for sickness or confinement benefit with which practitioners are familiar, though it notes in passing that some doctors might, to their own benefit, acquaint themselves closely with the regulations The committee rejected a proposal that there should be a list of specified conditions for which the doctors might issue certificates of more than one week's duration from the beginning Because under its terms of reference its deliberations were restricted to certification for National Insurance purposes, the committee expressed no opinion on suggestions that modifications of the National Insurance certificates might simplify their use for other purposes This is a pity, for the demand for extra certificates wastes time in practice The Ministry might be invited to think again on this point, giving its committee a wider brief

APPROVED NAMES FOR DRUGS

THE British Pharmacopœia Commission has issued the following new supplementary list of approved names

Approved name	*Other names*
Amphotericin	Polyene antibiotics isolated from a strain of a *Streptomyces* species, referred to as *Streptomyces nodosus* (specific substances are designated by a terminal letter, thus, Amphotericin B) Fungizone is Amphotericin B
Benzonatate	2-(ω-Methoxypolyethyleneoxy)ethyl *p* butylamino-*benzoate* Tessalon
Benzthiazide	3-Benzylthiomethyl-6-chloro-7-sulphamoylbenzo-1 2 4-thiadiazine 1 1-dioxide Fovane
Chlormidazole	1-*p*-Chlorobenzyl-2-methylbenzimidazole
Chlorzoxazone	5-Chlorobenzoxazolin-2-one
Cinnarizine	1-*trans*-Cinnamyl-4-diphenylmethylpiperazine
Diethylpropion	α-Diethylaminopropiophenone Tenuate is the hydrochloride
Guanethidine	1-(2-Guanidinoethyl)aza*cyclo*octane Ismelin is the sulphate
Itramin tosylate	2-Nitratoethylamine toluene-*p*-sulphonate Nilatil
Methandienone	*17β-Hydroxy-17α-methylandrosta-1 4-dien-3-one* Dianabol
Methdilazine	10-(1-Methyl-3-pyrrolidinylmethyl)phenothiazine
Metronidazole	1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole Flagyl
Nealbarbitone	5-Allyl-5-neopentylbarbituric acid Censedal, Nevental
Paromomycin	An antibiotic produced by *Streptomyces rimosus forma paromomycinus* D-Glucosaminedeoxystreptamine D ribosediamino-hexose *Humatin is the sulphate*
Phenethicillin	6-(α-Phenoxyproprionamido)penicillanic acid (1-Phenoxyethyl)penicillin Broxil is the potassium salt
Pralidoxime iodide	Picolinaldoxime methiodide Protopam
Sodium ipodate	Sodium β-(3-dimethylaminomethylenamino-2 4 6-triiodophenyl)propionate Biloptin
Spironolactone	β-(7α-Acetylthio-17β-hydroxy-3-oxoandrost-4-en-17α-yl)propionic acid lactone Aldactone
Sulphinpyrazone	1 2-Diphenyl-4-(2-phenylsulphinylethyl)pyrazolidine-3 5-dione Anturan
Thioproperazine	2-Dimethylsulphamoyl-10-[3-(4-methylpiperazin-1-yl)-propyl]phenothiazine Majeptil is the methanesulphonate

Proprietary name	*Approved name reference*	*Proprietary name*	*Approved name reference*
Aldactone	Spironolactone	Anturan	Sulphinpyrazone
Biloptin	Sodium ipodate	Broxil	Phenethicillin
Censedal	Nealbarbitone	Dianabol	Methandienone
Flagyl	Metronidazole	Fovane	Benzthiazide
Fungizone	Amphotericin	Humatin	Paromomycin
Ismelin	Guanethidine	Majeptil	Thioproperazine
Nevental	Nealbarbitone	Nilatil	Itramin tosylate
Protopam	Pralidoxime	Tenuate	Diethylpropion
Tessalon	Benzonatate		

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[1] Ministry of Health and General Register Office *Report on Hospital Inpatient Enquiry* Part I H M Stationery Office 1960 p 14 *1s 6d*

[1] Doctors and Midwives' Certificates for National Insurance Purposes report of the National Insurance Advisory Committee H M Stationery Office 1960 Pp 12. 1s

A YOUNGHUSBAND TYPE?

In 1956 the Manchester Regional Hospital Board, with the helpful connivance of such interested parties as the University of Manchester, the Ministry of Health, and the Institute of Almoners, started an experimental training scheme for "hospital welfare workers" Almoners were scarce in the region, and it was hoped that by this means people with suitable personality and experience who did not necessarily have academic qualifications could be trained to deal independently with the straightforward needs of patients The almoners, as qualified case workers, could reserve their time and energy for patients with complex personal problems Since then the Younghusband Committee have included in their proposed revision of the structure of the social services a "general purpose social worker" who might well have a good deal in common with Manchester's hospital welfare worker, though his, or her, activities would of course not be limited to the hospital Manchester's experimental training course may thus prove to have been an involuntary modest pilot scheme, and the report of its first three years by Mrs Gray, the tutor for the scheme, will find attentive readers outside the Manchester region [1]

The course was open to men and women between twenty-one and forty-five though older people were considered There was room for only 8–10 students, but despite many inquiries (968 in 1958), the selection committee found no great untapped reserve of potentially good workers and could not have filled more places had they been available The course lasted twelve months and included practical work in almoners' departments as well as theoretical studies The trainees were paid a salary of £300 p a. Of the 12 who successfully completed the course in the first two years 10 are now working—5 with almoners and 5 on their own Even with this small number there seem to have been difficulties in arranging for practical work. At the end of their course workers were allocated to hospitals within the region by a subcommittee of the board on the recommendation of the tutor This system has defects as well as merits, and though perhaps appropriate at this experimental stage, it would presumably be discarded in any permanent scheme

POISONS LIST

The following substances (and their salts or esters) have been added to part I of the Poisons List [2]

Acetylcarbromal.
Androgenic and oestrogenic substances
Benzoestrol.
Derivatives of stilbene, dibenzyl or naphthalene with oestrogenic activity
Steroid compounds with androgenic or oestrogenic activity
Azacyclonol
Benactyzine
Benzethidine
3-Benzylhydrazinocarbonyl-5 methylisooxazole
Bromvaletone
Captodiame
Carbromal
2-*p*-Chlorophenyl-3-methylbutane-2 3-diol
Chlorpropamide.
Cyclophosphamide
Dimenoxadole
Furethidine
4-Hydroxymethyl-2 2-diisopropyl-1 3-dioxolan
Hydroxyzine
Imipramine
Mannomustine
Mephenesin
Meprodamate
Metformin
Methocarbamol
α-Methyl-phenethylhydrazine
Methyl phenidate
Norcodeine
Normorphine.
Phenazocine
Phenelzine
Phenformin
Phenmetrazine
Pipradrol
Thalidomide.
Zoxazolamine
Alkaloids
  Rauwolfia, alkaloids of
Anti-histamines
  Buclizine
  (*p*-Chlorophenylpyrid-2-yl-methyl) 2-dimethylaminoethyl ether
  1-(4-*p*-Chlorophenyl-3-pheny-but-2-enyl)-pyrrolidine
  Chlorpheniramine
  Clemizole
  Cyclizine.
  1-Dimethylamino-3-phenyl-3-(2-pyridyl)-propane
  Diphenylpyraline
  Doxylamine
  Isothipendyl
  Mebhydrolin
  Meclozine
  Thenalidine
  Triprolidine

For the item ' 3-(10-Phenothiazinyl)propane substituted in the 1-position, its salts, derivatives of 3-(10-Phenothiazinyl)propane substituted in the 1-position, their salts there shall be substituted the item Phenothiazine derivatives of, their salts, except promethazine, its salts and its molecular compounds

The Poisons Rules [3] have been consolidated and amended

University of Birmingham

The following titles have been conferred

Dr C R Lowe, reader in social medicine, Dr J M French, honorary reader in medicine, Dr J P Bull, honorary lecturer in the department of experimental medicine

Mr R J Mills has been appointed William E Dunn research associate in the department of medicine and Mr B Atkins research associate in the department of pædiatrics and child health

University of Glasgow

Dr C M Fleming has been appointed to the recently established chair of administrative medicine

Dr Fleming, who is 56 years of age, was educated at Hillhead High School and the University of Glasgow where he graduated M.A. in 1924, M B in 1929, and M D in 1933 He became a member of the Royal College of Physicians of Edinburgh in 1945 and a fellow in 1952, he was elected a fellow of the Royal Faculty of Physicians and Surgeons of Glasgow in 1959 Dr Fleming, who has been dean of the faculty of medicine in the university since he became reader in administrative medicine early last year, joined the Department of Health for Scotland as a regional medical officer in 1937, and became a principal medical officer in 1946

Dr A C Forrester has been appointed reader in anæsthetics and Dr E Hutchinson reader in hæmatology

Royal College of Surgeons of England

At a meeting of the council on May 12, with Sir James Paterson Ross, the president, in the chair, Dr Frankis Evans, Surgeon Captain J L S Coulter, Dr E F Scowen, and Prof E C Amoroso were admitted to the fellowship after election

The Jacksonian prize was presented to Mr Geoffrey Slaney and the Lady Cade medal was awarded to Group-Captain Ralph Coburn Jackson

Postgraduate diplomas and diplomas of membership were conferred on the candidates named in the report of the comitia of the Royal College of Physicians (*Lancet*, May 7, 1960, p 1033)

British Pædiatric Association

The following officers have been appointed

President, Prof A V Neale, president elect, Prof A A Moncrieff, treasurer, Prof A G Watkins, secretary, Dr E W Hart

Society of Apothecaries of London

Faculty of the History of Medicine and Pharmacy—Dr K. D Keele will give the first annual students' lecture on Thursday, June 2, at 5.30 P M at Apothecaries' Hall, Black Friars Lane, E C 4 His subject will be William Harvey—Pioneer of Medical Science Admission is by ticket, obtainable from the deans of the medical schools

Oliver Bird Lecture

Dr J Parizek, from the Laboratory of Physiology and Pathophysiology of Metabolism, Prague, will give this lecture on Thursday, May 26, at 5 P M at Guy's Hospital Medical School, London, S E 1 He will speak on sterilisation of the male by cadmium salts

Patrick Buxton Memorial Prize

This has been endowed in memory of Prof P A Buxton, a former director of the department of entomology at the London School of Hygiene and Tropical Medicine The first award will be made in 1961 to past or present students or members of the staff of the school Further particulars may be found in our advertisement columns

Congress of European Organisation for Research on Fluorine and Dental Caries Prevention

This congress will be held from June 2 to 4 in Hamburg Speakers from this country will include Mr R Fearnhead, Prof A I Darling, Prof A B Macgregor, Mr J H Fremlin, and Mr F L Hardwick Particulars may be had from the secretariat of the congress, Hamburg 20, Martinistrasse 52, Universitätskrankenhaus Eppendorf, Zahn, M Kieferklinik (C II), Germany

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[1] Gray, Rosemary Training Scheme for Hospital Welfare Workers 1960 Pp 45 2*s* (From Manchester R.H B, Cheetwood Road Manchester 11)

[2] The Poisons List Order, 1960 S I 1960, no 698 H.M Stationery Office Pp 10 6*d*

[3] The Poisons Rules, 1960 S I 1960 no 699 H M Stationery Office Pp 44 1*s* 9*d*

Doctors in Malta

Doctors in the Government medical service of Malta, who have been on strike since May 2, returned to work on May 14 (*Times*, May 16) after an agreement was reached over an appointment to the post of deputy senior medical officer

Dental Ancillaries

A training course for dental hygienists started in Manchester last autumn Other training units are expected to be ready this year The General Dental Council's experimental training scheme for dental auxiliaries is planned to start in the autumn

World Congress on the Prevention of Occupational Risks

This congress, arranged by the National Safety Institute of France, will be held in Paris from May 22 to 27, 1961 Particulars may be had from the Institut National de Securite, Secretariat du III^{e} Congres mondial, 9, avenue Montaigne, Paris 8^{e}

European Congress of Child Psychiatry

This congress wil be held at the New School of Medicine, 45, rue des Saints Peres, Paris VI°, from Sept 16 to 20 The theme will be maturation A symposium on child psychoanalysis will be held at the end of the congress Further particulars may be had from the secretary-general, Dr D J Duche, Pavillon Clerambault, Hôpital de la Salpetriere, 47, boulevard de l'Hôpital, Paris XIII^{e}

Proposed New Hospital for North Hertfordshire

On May 4 the North West Metropolitan Regional Hospital Board met representatives of the Baldock, Hitchin, Letchworth and Stevenage councils and the Stevenage Development Corporation to outline their plans for the hospital services for the area It was proposed to build a new hospital with about 400 beds at Corey's Mill, Stevenage, which would serve the acute hospital needs of the area It would become a new Lister Hospital replacing the temporary wartime hospital in Hitchin Part of the present Lister Hospital would then become the geriatric hospital for the area and the North Herts Hospital would be reserved for maternity work The proposals would need the approval of the Ministry of Health

The National Hospital, Queen Square

The centenary celebrations of this hospital will be opened on Monday, June 20, at 11 30 A M, by Mr Derek Walker-Smith, the Minister of Health On the following day, June 21, at 10 45 A M the Duke of Edinburgh will visit the hospital Demonstrations and lectures will be given at the hospital from June 20 to 24 Neurologists from abroad who are taking part will include Dr Pearce Bailey (Bethesda, Maryland), Prof T Alajouanine (Paris), Prof H Gastaut (Marseilles), and Dr Chorobski (Warsaw) Dr Macdonald Critchley will give the centennial oration, in which he will speak on Jacksonian ideas and the future with special reference to aphasia Sir Charles Symonds the Gowers lecture (disease of mind and disorder of brain), and Prof Norman Dott the Victor Horsley lecture (brain, movement, and time)

By arrangement between the North East Metropolitan Regional Hospital Board and the Royal Free Hospital, some consultants and senior hospital medical officers are to attend the Royal Free Hospital for short postgraduate courses The idea behind the scheme is to promote closer cooperation between the pathology departments of teaching and non-teaching hospitals, and to give pathologists the opportunity of learning any techniques more usually found in a teaching hospital

Mr L T Morton, the librarian of the National Institute of Medical Research, Mill Hill, London, N W 7, has received the Marcia C Noyes award of the Medical Library Association of America

The United Hospitals Choir with the London Choral Orchestra will give a performance of Handel's Belshazzar on Tuesday, May 31, at 7 30 P M, in Chelsea Town Hall, London, S W 3 Tickets 5*s*, 3*s* 6*d*) may be had from Miss E Sorensen, South Hospital, Landor Road, S W 9, or at the door

The Biochemical Society will hold a joint meeting with the Société de Chimie Biologique at the Faculté de Pharmacie, Avenue de l'Observatoire, Paris 6^{e}, on Friday and Saturday, May 27 and 28

The Yorkshire Society of Anæsthetists will hold a meeting on Wednesday, June 8, at 8 30 P M at the General Infirmary at Leeds Dr Shila Ransom will speak on the role of the anæsthetist in the obstetric unit

The North of England Otolaryngological Society will hold a meeting with the Scottish Otolaryngological Society in Carlisle on Saturday, June 11, at 2 P M

Diary of the Week

MAY 22 TO 28

Monday, 23rd

WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, *St Mary's Hospital Medical School, W.2*
5 P M Dr P L Mollison The Role of Complement in Blood Group Reactions (Almroth Wright lecture)
POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W 12
4 P.M Prof E P Sharpey-Schafer Syncope.
MANCHESTER MEDICAL SOCIETY
9 P.M (Medical School, University of Manchester) *General Practice* Dr H W Ashworth Hobson's Choice (Presidential address)

Tuesday, 24th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 P.M *Medicine* Dr A St J Dixon Hyperuricæmic Nephropathy Dr C T Dollery Detection of Unilateral Renal Disease in Hypertension with Diodrast ^{131}I Dr A M Joekes Indications for Renal Biopsy
ST MARY S HOSPITAL MEDICAL SCHOOL, W 2
5 P M Mr Leonard Easton Historical Aspects and Modern Views of Management of Retained Placenta
INSTITUTE OF DERMATOLOGY, Lisle Street, W C.2
5 30 P M. Prof Gilbert Causey Observations on the Optical and Electron Microscopical Structure of the Skin

Wednesday, 25th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M Dr A F B Standfast Infection of Mice with *Bordetella* (*Hæmophilus*) *pertussis*
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Sir Russell Brock Aortic Stenosis
INSTITUTE OF DERMATOLOGY
5 30 P M Dr R. W Riddell Recent Advances in the Study of Ringworm
UNIVERSITY OF OXFORD
5 P.M (Radcliffe Infirmary) Prof Raoul Palmer Reconstructive Surgery of Fallopian Tubes (Litchfield lecture)
MANCHESTER MEDICAL SOCIETY
5 P.M (Medical School, University of Manchester) *Pathology* Prof Jethro Gough Recent Advances in the Pathology of Lung Diseases
ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH, 9, Queen Street, Edinburgh
5 P.M Mr F J Gillingham Stereotactic Surgery of the Brain—Therapy and Research (Morison lecture)

Thursday, 26th

UNIVERSITY OF LONDON
5.30 P M (King's College, Strand, W C 2) Prof P Waser (Zürich) The Cholinergic Receptor
UNIVERSITY COLLEGE, Gower Street, W C 1
5 P.M Dr S J Bach Metabolic Fate of Protein-nitrogen in the Mammal (First of two lectures)
POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M Prof M L Rosenheim Phæochromocytoma
INSTITUTE OF DERMATOLOGY
5 30 P M Dr P D SAMMAN Cutaneous Reticuloses
UNIVERSITY OF ST ANDREWS, Queen s College, Dundee
5 P.M Dr Ffrangcon Roberts Acceptance of the Scientific Method of Medicine—its Origin, Evolution, and Consequences

Friday, 27th

ROYAL SOCIETY OF MEDICINE
5 P.M *Pædiatrics* Dr J H Edwards, Dr D G Harnden, Prof L. S Penrose, Dr Paul Polani Human Chromosomes in Relation to Disease in Childhood
8 15 P.M. *Obstetrics and Gynæcology* Mr Frank Musgrove Gynæcological and Obstetrical Impressions of a Visit to the United States Miss M Moore White Uteroplasty in Infertility Mr D J MacRae, Mr T S M Barnett, Mr Norman Smyth Use of the Cardiophone in the Labour Ward
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr Ashton Miller Pædiatric Urology
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road W C.1
5 30 P.M Mr George Qvist Surgery of the Lower Œsophagus
INSTITUTE OF NEUROLOGY, *The National Hospital*, Queen Square W C 1
4 30 P M Mr Valentine Logue Surgical Management of Cerebral Aneurysms
ROYAL STATISTICAL SOCIETY
5.30 P M (London School of Hygiene and Tropical Medicine Keppel Street, W C.1) *Medical Section* Dr N T J Bailey, Mr T H Hollingsworth, Dr A E Maxwell Related Variables in Medical Statistics

Saturday, 28th

MEDICAL ASSOCIATION FOR THE PREVENTION OF WAR
2.30 P.M (45, Russell Square, W C.1) Symposium on Present-day Significance of Medical Science in Relation to War Prevention

The Lancet · Saturday 28 May 1960

CHRONIC RINGWORM INFECTION OF THE SKIN AND NAILS TREATED WITH GRISEOFULVIN

REPORT OF A THERAPEUTIC TRIAL

BRIAN RUSSELL
M D Lond , F.R.C.P , D.P.H
CONSULTANT DERMATOLOGIST

W FRAIN-BELL
M.D St And , M.R.C.P.E
RESEARCH FELLOW

C J STEVENSON
M.D Lond , M R.C.P
SENIOR MEDICAL REGISTRAR

R. W RIDDELL
M.D Lond , F.R.C.P.E
SENIOR LECTURER

N DJAVAHISZWILI
B Sc Lond
RESEARCH ASSISTANT

MEDICAL MYCOLOGY DIVISION
INSTITUTE OF DERMATOLOGY,
ST JOHN'S HOSPITAL FOR DISEASES OF THE SKIN, LONDON, W C 2

S L MORRISON
M B St. And., D.P H
MEMBER OF SCIENTIFIC STAFF, MEDICAL RESEARCH COUNCIL
SOCIAL MEDICINE RESEARCH UNIT, LONDON HOSPITAL, LONDON, E.1

Trichophyton rubrum is responsible for the most intractable form of ringworm infection of the skin and nails, a condition in which spontaneous remissions are rare Though many antibiotics and other chemical substances have considerable in-vitro fungistatic activity against the dermatophytes, none have eradicated *T rubrum* from infected patients when applied to the skin surface Prior to griseofulvin, none of these fungistatic agents proved effective against various forms of ringworm when given by mouth Consequently, treatment of *T rubrum* infection has consisted in achieving as much physical improvement of the skin condition as possible by applying locally an antifungal substance combined with desquamating and penetrating agents, while keeping thinly filed any infected nails which may be present Surgical avulsion of affected nail plates does not preclude infection and deformity occurring in the nails as they regrow

Griseofulvin was isolated in 1939 by Oxford, Raistrick, and Simonart from *Penicillium griseofulvum* Dierkx, though its potentialities as a fungistatic agent were not appreciated until eight years later

In 1946, Brian et al described the inhibitory effects on the hyphæ of certain fungi of a metabolite (" curling factor ") from *Penicillium janczewskii* Zal, and in 1947 Grove and McGowan showed this substance and griseofulvin to be one and the same In the ten years which followed, griseofulvin was used to combat fungous infections of plants, but it was not until 1958 that Gentles demonstrated its efficacy by mouth in controlling experimental ringworm in guineapigs Riehl (1958) and Williams et al (1958) reported in the same year that griseofulvin was effective in human disease due to dermatophytes The toxicity of griseofulvin was in question for a time following the observation by Paget and Walpole (1958) that it appeared to possess a colchicine-like action on mitoses when injected intravenously in large doses into animals Up to the present time, oral administration in man has given no evidence that important side-effects occur

From these preliminary papers it appeared that griseofulvin might well be a real advance in treatment Accordingly, in January of last year, 11 patients were started on griseofulvin These patients were admitted * to the inpatient department of St John's Hospital for Diseases of the Skin for the first month of treatment Early results confirmed the observations of Williams et al (1958) and no toxic side-effects were observed (Results during one year's treatment are reported below)

It was then decided to treat a group of outpatients with griseofulvin over a long period The object was to discover how efficacious the drug was, both in promoting clinical cures at various sites and in its mycological effects At the same time, it seemed opportune to undertake a controlled trial to compare the results of treatment, and any side-effects, with those in a group of patients given a dummy treatment This period, soon after the introduction of the drug, was the *only* time when such a trial was likely to be carried out

The Therapeutic Trial

The object of this trial was to measure the effects, both therapeutic and toxic, of prolonged therapy with the drug by comparing a group of patients treated with griseofulvin with a control group given dummy tablets A double-blind form of trial was used to ensure that bias did not affect the results Neither patients nor physicians were to know which participants were being treated with griseofulvin and which with the dummy No local treatment of lesions was given

When the trial was planned we did not know how long a course of treatment would be needed for clinical cure, but it was thought that in most treated patients improvement should be seen within four months For the purposes of the trial, " definite clinical improvement " at any site was accepted as the criterion of success This, in fact, amounted to unequivocal progressive improvement of one or more affected sites

To limit the trial to the minimum number of patients, and thus to make sure that as few as possible received the placebo, a sequential analysis of the results was planned (see statistical appendix) This analysis was used to indicate when the intake of new patients could be stopped and not to analyse the full results (Armitage 1958) When the intake was stopped, those patients already in the trial continued until their four months on griseofulvin or placebo tablets was completed Thereafter, control patients were given the active treatment

METHOD

Starting in February, 1959, between 10 and 15 patients known to be suffering from chronic ringworm infection joined the trial weekly

They were told that the effective dosage of a new drug was being tested and that some patients would receive small doses and others large The results of clinical examination of the skin and nails, a full blood-count, and mycological assessment were recorded on a standard form, and a serial number was allotted Patients were then sent to the pharmacy, where appropriate tablets were issued The pharmacist had a prearranged list allocating patients at random, according to their serial numbers, to treated and control groups

Those in the treated group were given tablets sufficient for a daily dosage of 1 5 g of griseofulvin, and control

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[*] 12 patients were admitted but one developed scarlet fever after only eight days treatment

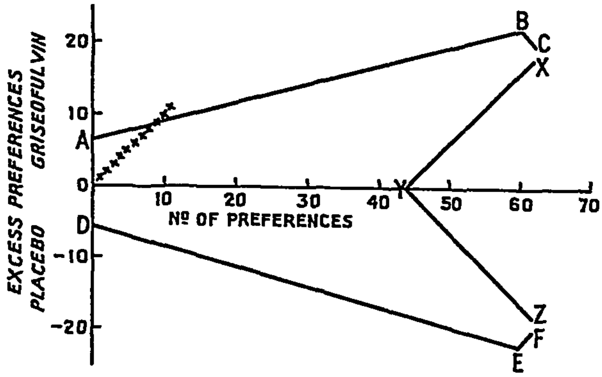

Chart for sequential analysis of results

Horizontal scale records the number of pairs showing preference, vertical scale records the number of preferences for griseofulvin minus the number of preferences for the placebo Path moves one unit "north-east" when treated member of a pair is improved and one unit "south-east" when control member is improved

A path reaching boundary ABC indicates a significant ($P<0 05$) advantage to griseofulvin, one reaching DEF would point to a significant advantage to the dummy treatment, while a path reaching XYZ would show that there was no real difference between griseofulvin and the dummy

patients were given a similar supply of inert tablets of the same appearance but containing only tribasic calcium phosphate (215 5 mg), starch (55 5 mg), and magnesium stearate (4 5 mg) Patients were seen two weeks later and again at intervals of four to eight weeks Each patient's progress and subjective and objective observations were recorded at every visit, when a further supply of either griseofulvin or the placebo was provided by the pharmacist

The first analysis was made to decide when to stop the intake of patients This sequential analysis was based on the first finding by either of the two assessing physicians of "definite clinical improvement" In the analysis, treated and control patients were grouped in pairs, and only pairs showing preference were plotted on a prepared chart (see figure) A result was recorded when either the treated or the control member was improved and the other was not, if both were improved or both not improved, no action was taken When the treated member of the pair was improved, a cross was plotted one unit "north-east" of the origin at 0 Had there been the opposite result in a pair—the control member improved and the treated not improved—the next cross would have been plotted one unit "south-east" of the preceding one The boundary lines are drawn in such a way that if the plotted points reach the line ABC, the treated group is showing an advantage over the control group significant at the 5% level and the intake of new patients in the trial can be stopped

TABLE I—FUNGI RESPONSIBLE FOR DISEASE IN 76 PATIENTS WHO COMPLETED 4 MONTHS IN TRIAL

Organism	Number of patients
Trichophyton rubrum	70
T rubrum and *T mentagrophytes* var *interdigitale*	1
T rubrum and *Epidermophyton floccosum*	1
T mentagrophytes var *interdigitale*	3
E floccosum	1

RESULTS

Sequential Analysis

When the results were plotted in this way, the points fell on a straight line which crossed line ABC (see figure) Though the intake of patients could, in fact, have stopped after plotting the results for the first 9 pairs showing preference, the intake was extended beyond this number It was overcautious to continue to accept a few new patients after the plotted line reached ABC, but since this was apparently the first application of a restricted sequential plan to a trial with a comparatively long response time, and because the first results were so strikingly favourable, it was thought wise to err in this way When entry into the trial was stopped, 76 patients had been registered and were receiving either griseofulvin or dummy tablets These patients were allowed to complete four months in the trial before results in the treated and control groups were compared

TABLE II—AGE OF 76 PATIENTS

Years	Treated	Control
11–20	2	2
21–30	7	7
31–40	7	11
41–50	9	11
51–60	8	8
61–70	4	0
Total	37	39

TABLE III—DURATION OF INFECTION OF 76 PATIENTS

Years	Treated	Control
0–5	11	13
6–10	11	14
11–15	4	5
16–20	7	4
21–25	2	0
30+	2	3
Total	37	39

Comparison after Four Months

The 76 patients were 41 men and 35 women, and 72 of them were infected with *T rubrum* (table I) Their ages and the duration of their disease are shown in tables II and III

Before completing four months in the trial, 4 treated and 8 control patients had left the investigation for one reason or another, leaving 33 treated and 31 control patients for comparison (table IV)

Using the criterion of "definite clinical improvement" as described above, 31 of the 33 treated patients were improved after four months while 2 were not After the same period, only 1 of 31 control patients was improved while 30 were not (table va) With such a clear difference between the groups no calculation of "significance" is necessary Further comparisons are given in tables vb and c

Only 2 patients receiving griseofulvin were not improved at the end of four months

In one of these (no 62), improvement was slight and difficult to assess up to the sixteenth week, though by the twenty-second week it was definite and progressive The other patient (no 44) showed some improvement at the sixteenth week, but this was indefinite, since the infection was virtually confined to the

TABLE IV—DISPOSAL OF PATIENTS 4 MONTHS AFTER ENTERING THE TRIAL

Category	No entered	No defaulted *	No treatment discontinued †	Total no for analysis
Treated with griseofulvin	37	2	2	33
Controls	39	6	2	31
Total	76	8	4	64

* Defaulters 3 in the first month, 3 in the second month, 1 in the third month, and 1 in the fourth month

† Treatment discontinued 2 developed rashes, 1 became pregnant, and 1 required surgery

1 control patient defaulted after assessment at four months

toenails, by the twenty-fourth week marked improvement was seen

Only one patient in the control group was "improved" after four months on dummy tablets This case (no 59) improved before the sixteenth week, the improvement being confined to the fingernails

Other Clinical Observations

Symptoms and signs which might possibly be attributed to side-effects were recorded in the first four months in 9 of the 37 griseofulvin patients and in 9 of the 39 controls (table VI)

TABLE V—COMPARISON OF TREATED AND CONTROL PATIENTS AFTER 4 MONTHS

(a) Definite clinical improvement at any site

—	Improved	Not improved	Total
Treated	31	2	33
Control	1	30	31
			64

(b) Skin of hands returned to normal

—	Skin normal	Skin still affected	Total
Treated	16	5	21
Control	0	20	20
			41

(c) Skin of feet returned to normal

—	Skin normal	Skin still affected	Total
Treated	21	7	28
Control	0	28	28
			56

Monocyte-counts above 500 per c mm occurred at one time or another in 24 of the 37 patients receiving griseofulvin and in 26 of the 39 patients receiving the inert tablets, and counts above 1000 per c mm occurred in 7 of the patients receiving griseofulvin (maxima 1880, 1740, 1720, 1580, 1430, 1140, 1140 per c. mm) compared to 5 receiving the inert tablets (maxima 2110, 1440, 1280, 1170, 1100 per c mm)

TABLE VI—"SIDE-EFFECTS" UP TO 16 WEEKS IN DOUBLE-BLIND TRIAL

Symptom or sign	Patients receiving griseofulvin (37)	Patients receiving inert tablets (39)
Headache	3	1
Dyspepsia	1	1
Abdominal discomfort	1	2
Vomiting, nausea	0	2
Diarrhœa	1	2
Ulcers in mouth	0	1
Cramps in limbs	2	0
Flushing of face	0	1
Drowsiness	0	1
Fever	1	0
Lassitude	1	0
Nails more brittle	0	1
Rashes or itching	3	4

RESULTS OF LONG-TERM TREATMENT WITH GRISEOFULVIN

Treated Group

Patients in this group have now been treated with griseofulvin for periods ranging from seventeen to fifty-two weeks The sites of infection in these 33 patients were hands (21 patients), feet (28), fingernails (22) and toenails (32)

Initial improvement in skin lesions of the hands was noted in most instances by the sixth week, but this was delayed in a few cases until the eighth week or later and in 1 case until the twenty-second Skin lesions of the feet showed initial improvement after similar periods (table VIIa)

TABLE VII—PROGRESS OF SKIN LESIONS IN TREATED GROUP

(a) First improvement recorded at

Weeks of treatment	2	3	4	6	8	10	12—22	24
Hands (21 patients)		1	9	6	3		1 1	
Feet (28 patients)	1	1	11	7	6	1		1

(b) Returned to normal by

Weeks of treatment	8	10	12	14	16	18	20	22	24—28—36
Hands (21 patients)	4	3	4	2	3	1	1		2 1
Feet (28 patients)	3	3	9	1	5	1	2		3 1

By the sixteenth week the skin of the hands had returned to normal appearance in 16 (76%) of 21 patients, and the skin of the feet in 21 (75%) of 28 patients (table VIIb) All the patients had normal skin within thirty-six weeks of treatment

The time required for improvement of nails to become obvious differed considerably for hands and feet Of the 22 patients with affected fingernails, all but 2 had improved by the twelfth week, whereas only 20 of the 32 patients with toenail infection had done so (table VIIIa) Similarly, fingernails regrew normally much more quickly than toenails (table VIIIb) For example, by the end of the ninth month 16 (80%) of 20 patients ,with fingernail infection had regrown normal nails, whereas only 3 (12%) of 26 patients with toenail lesions had done so Furthermore, after eleven months' treatment, the toenails of only 6 patients out of 17 (35%) had regrown normally

TABLE VIII—PROGRESS OF NAIL LESIONS IN TREATED GROUP

(a) First improvement recorded at

Weeks of treatment	4	6	8	10	12	14	16	18	20	22	24
Fingers (22 patients)	4	3	5	4	4	1				1	
Toes (32 patients)	2	1	10		7	3	5	1	2		1

(b) Returned to normal by

Weeks of treatment	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	N Y N
Fingers (22 patients)	1	1			1	1	1	2	3	1	3	1	1		1			5*
Toes (32 patients)							1		1	1					1	1	1	26†

N Y N =Not yet normal * 2 of the 5 received <36 weeks' treatment
† 15 of the 26 received < than 44 weeks treatment, and 6 of these <36 weeks' treatment

Control Group

All the 30 control patients who received dummy tablets at first but who were later given griseofulvin showed

TABLE IX—PROGRESS OF SKIN LESIONS IN 30 CONTROL PATIENTS SUBSEQUENTLY GIVEN ACTIVE TREATMENT

First improvement recorded at

Weeks of treatment	2	3	4	6	8	10
Hands (20 patients)	2	1	15	1	1	
Feet (28 patients)	2	1	17	4	3	1

TABLE X—PROGRESS OF NAIL LESIONS IN 30 CONTROL PATIENTS SUBSEQUENTLY GIVEN ACTIVE TREATMENT

First improvement recorded at

Weeks of treatment	2	4	6	8	10	12	14	16	18	20	22
Fingers (18 patients *)	1	3	4	7	1	2					
Toes (27 patients)		1	2	9	7	2	3	2			1

* One other patient showed improvement while receiving the placebo tablets

TABLE XI—FIRST IMPROVEMENT (a) AND CLEARING (b) OF LESIONS (WEEKS AFTER STARTING ACTIVE TREATMENT)

Case	Sex Age	Fungus type	Duration of disease (years)	Active treatment (weeks)	Skin sites			Nails	
					Hand	Feet	Other	Finger	Toe
1*	F 32	I	10	26	N.L.	(a) 4 (b) 10	N.L.	N.L.	N.L.
2	F 55	R	20	26	(a) 4 (b) 12	(a) 4 (b) 12	N.L.	(a) 4 (b) 27‡	(a) 4 (b)
3	F 46	R	15	52	N.L.	(a) 4 (b) 16	N.L.	(a) 4 (b) 32	(a) 16 (b)
4*	M 26	R	2	Defaulted after 4 weeks on control tablets					
5*	F 36	R	10	30	(a) 4 (b) 12	(a) 4 (b) 12	N.L.	(a) 6 (b)	(a) 12 (b)
6‡	F 46	R	15	32	(a) 4 (b) 9	(a) 4 (b) 9	N.L.	(a) 8 (b)	(a) 10 (b)
7	M 33	R	3	51	(a) 6 (b) 11	(a) 6 (b) 11	N.L.	N.L.	(a) 6 (b) 39
8	F 30	R	14	50	(a) 4 (b) 8	(a) 4 (b) 12	Knee & shin (a) 3 (b) 4	(a) 10 (b)	(a) 12 (b)
9*	M 39	R	18	Defaulted after 4 months on control tablets					
10	M 19	R	5	32	(a) 8 (b) 16	(a) 8 (b) 16	N.L.	(a) 12 (b) 28	(a) 8 (b) 28
11*	M 45	I	2	29	(a) 4 (b) 10	(a) 4 (b) 10	N.L.	N.L.	N.L.
12*	M 27	R	2	29	(a) 4 (b) 8	(a) 4 (b) 8	N.L.	(a) 4 (b) 22	(a) 10 (b)
13	M 39	R	10	50	(a) 4 (b) 12	(a) 6 (b) 12	N.L.	(a) 8 (b) 34	(a) 8 (b)
14	F 49	R	7	49	(a) 6 (b) 8	(a) 6 (b) 8	N.L.	(a) 6 (b)	(a) 8 (b)
15*	M 57	R	7	30	(a) 4 (b) 6	(a) 4 (b) 10	N.L.	(a) 8 (b)	(a) 10 (b)
16*	F 45	R	16	28	N.L.	(a) 8 (b) 12	N.L.	N.L.	(a) 8 (b)
17	M 28	R	2	17	(a) 3 (b) 10	(a) 3 (b) 10	N.L.	N.L.	(a) 8 (b) 24§
18	F 51	R	2½	Defaulted after 3 months treatment					
19*	F 45	R	30	Defaulted after 4 weeks on control tablets					
20	M 25	R	20	48	N.L.	(a) 10 (b) 16	Shin (a) 10 (b) 16	N.L.	(a) 8 (b)
21*	M 44	R	11	28	(a) 2 (b) 4	(a) 4 (b) 12	N.L.	(a) 12 (b)	(a) 14 (b)
22*	F 45	R	16	Defaulted after 2 weeks on control tablets					
23	M 37	R	16	44	(a) 4 (b) 8	(a) 4 (b) 8	N.L.	(a) 4 (b) 20	(a) 12 (b) 42
24	M 23	R	5	46	(a) 8 (b) 14	(a) 8 (b) 14	N.L.	(a) 8 (b) 31	(a) 16 (b)
25*	M 25	R	3	Defaulted after 3 weeks on control tablets					
26	M 47	R	5	24	N.L.	N.L.	Neck (a) (b) 2	N.L.	(a) 4 (b)
27*	M 54	R—F	2	Defaulted one visit only (control tablets)					
28	M 62	R	6	47	(a) 6 (b) 15	(a) 6 (b) 11	N.L.	(a) 6 (b) 26	(a) 18 (b)
29*	F 25	R	7	20	N.L.	(a) 4 (b) 8	N.L.	N.L.	(a) 8 (b)
30	M 53	R	3	Stopped treatment—surgical operation					
31*	F 60	R	15	30	(a) 8 (b) 12	(a) 10 (b) 16	N.L.	(a) 8 (b)	(a) 14 (b)
32	M 31	R	3	27	(a) 4 (b) 10	(a) 4 (b) 10	N.L.	(a) 4 (b) 21	(a) 8 (b)
33*	F 30	R	8	28	N.L.	(a) 4 (b) 10	N.L.	N.L.	(a) 8 (b)
34*	M 53	R	5	Defaulted after 5 weeks on control tablets					
35	F 37	R	16	50	(a) 4 (b) 10	(a) 4 (b) 10	N.L.	(a) 9 (b) 26	(a) 12 (b) 30
36	F 21	R	6	49	(a) 12 (b) 16	N.L.	N.L.	(a) 13 (b) 36	(a) 16 (b) 44
37*	F 45	R	30	32	N.L.	(a) 8 (b) 12	N.L.	N.L.	(a) 8 (b)
38*	F 31	R	7	Cyesis—stopped "treatment" (control tablets)					
39	M 37	R+I	10	45	(a) 4 (b) 36	(a) 4 (b) 12	N.L.	(a) 6 (b)	(a) 4 (b)
40*	F 16	R	2	28	(a) 4 (b) 4	N.L.	N.L.	N.L.	N.L.
41	M 25	R	10	46	(a) 6 (b) 13	(a) 6 (b) 15	N.L.	(a) 10 (b) 24	(a) 14 (b)
42*	M 58	R	40	24	(a) 4 (b) 16	(a) 4 (b) 20	N.L.	(a) 10 (b)	(a) 16 (b)
43	M 42	R	30	44	N.L.	(a) 4 (b) 24	"Ide" did not clear	N.L.	(a) 12 (b)
44	F 52	R	15	38	N.L.	N.L.	N.L.	N.L.	(a) 16 (b)
45*	F 34	R	18	28	(a) 4 (b) 20	(a) 4 (b) 20	N.L.	(a) 8 (b) 21	(a) 22 (b)
46*	F 32	R	15	24	(a) 2 (b) 8	(a) 2 (b) 8	N.L.	(a) 2 (b) 10	(a) 10 (b)
47	F 26	R	8	43	N.L.	(a) 8 (b) 12	N.L.	N.L.	(a) 20 (b)
48	M 33	R	15	44	N.L.	(a) 2 (b) 8	N.L.	N.L.	(a) 8 (b)
49*	F 39	R	14	22	(a) 4 (b) 8	(a) 4 (b) 14	N.L.	(a) 5 (b)	(a) 9 (b)
50*	M 55	R	7	22	(a) 4 (b) 12	(a) 8 (b) 14	N.L.	(a) 12 (b)	(a) 16 (b)
51	F 53	R	9	Defaulted after 2 months' treatment					
52	M 44	R	30	42	(a) 8 (b) 20	(a) 8 (b) 20	N.L.	(a) 12 (b) 40	(a) 12 (b)
53*	F 52	R	8	"Treatment" stopped—skin rash (on control tablets)					
54	M 69	R	7	42	(a) 6 (b) 24	(a) 6 (b) 24	N.L.	(a) 10 (b) 30	(a) 16 (b)
55*	M 39	R	4	13	N.L.	(a) 6 (b) 8	N.L.	(a) 8 (b) 13	(a) 11 (b)
56*	M 35	R	5	22	(a) 4 (b) 8	(a) 4 (b) 12	N.L.	(a) 6 (b)	(a) 9 (b)
57	M 46	R	17	40	(a) 6 (b) 18	(a) 6 (b) 18	N.L.	(a) 11 (b) 28	(a) 20 (b)
58	M 46	R	25	40	N.L.	(a) 4 (b) 12	N.L.	(a) 8 (b) 12	(a) 8 (b)
59*	F 20	R	7	20	N.L.	N.L.	N.L.	(a) † (b)	(a) 14 (b)
60	F 62	R	1½	36	(a) 4 (b) 8	(a) 8 (b) 20	N.L.	(a) 12 (b) 32	(a) 24 (b)
61*	F 41	R	2	20	(a) 6 (b) 12	(a) 6 (b) 12	N.L.	(a) 8 (b)	(a) 10 (b)
62	M 53	I	5	32	(a) 22 (b) 24	(a) 24 (b) 28	N.L.	(a) 22 (b)	N.L.
63*	M 29	R	7	12	N.L.	(a) 6 (b)	N.L.	N.L.	(a) 7 (b)
64	F 51	R	25	37	N.L.	N.L.	N.L.	N.L.	(a) 8 (b)
65*	M 56	R	3	10	(a) 4 (b) 12	(a) 4 (b)	N.L.	(a) 4 (b) 12	(a) 4 (b)

R = *Trichophyton rubrum*
I = *T. mentagrophytes* var. *interdigitale*
F = *Epidermophyton floccosum*

* On control tablets initially
† Fingernails improved on control tablets
‡ Stopped treatment at 26 weeks

§ Stopped treatment at 17 weeks but observed at 24 weeks
N.L. = no lesion
(b) = not yet cleared

TABLE XI (*continued*)—FIRST IMPROVEMENT (a) AND CLEARING (b) OF LESIONS (WEEKS AFTER STARTING ACTIVE TREATMENT)

Case	Sex Age	Fungus type	Duration of disease (years)	Active treatment (weeks)	Skin sites			Nails	
					Hand	Feet	Other	Finger	Toe
66	F 66	R	6	Treatment stopped—rash					
67*	F 44	R	10	21	(a) 3 (b)	(a) 3 (b) 8	N.L.	(a) 3 (b)	(a) 6 (b)
68	M 48	F	18	39	N.L.	(a) 4 (b) 24	N.L.	N.L.	(a) 14 (b)
69*	M 34	R	10	12	(a) 4 (b)	(a) 4 (b)	N.L.	(a) 6 (b)	(a) 8 (b)
70	M 19	R	4	29	N.L.	N.L.	N.L.	(a) 8 (b) 14	(a) 8 (b)
71*	M 41	R	9/12	18	N.L.	(a) 2 (b) 8	N.L.	N.L.	(a) 8 (b)
72*	M 38	R	4	18	N.L.	(a) 4 (b) 8	N.L.	N.L.	(a) 8 (b)
73	F 41	R	8	28	(a) 4 (b) 12	(a) 8 (b) 12	N.L.	(a) 8 (b)	(a) 12 (b)
74	F 52	R	20	28	N.L.	(a) 4 (b) 16	N.L.	N.L.	(a) 12 (b)
75*	F 28	R	10	12	(a) 4 (b) 8	(a) 4 (b) 8	N.L.	(a) 8 (b)	(a) 8 (b)
76*	M 44	R	10	16	(a) 4 (b) 12	(a) 6 (b) 12	N.L.	N.L.	(a) 6 (b)

improvement following the active therapy (tables IX and X) Sites of infection in these patients were hands (20 patients), feet (28), fingernails (19), and toenails (27)

The detailed clinical data for the 76 patients in the double-blind trial are given in table XI

Inpatient Group

11 patients have now been treated for a year, after an initial month in hospital Of these patients, 9 were infected with *Trichophyton rubrum* and 2 with *T mentagrophytes* var *interdigitale*

Initially 8 of the 11 had dystrophic fingernails The fingernails of 6 of these returned to normal appearance and became negative mycologically This occurred in five months in 1 case, seven months in 3, and eight months in 2 The nails of the remaining 2 patients showed slight dystrophy after one year, but fungus could not be found in them after seven months of treatment (table XII)

Initially all the 11 had dystrophic toenails One of these patients became clinically normal after seven months and another after nine in the former fungus was demonstrable in the nails up to one year, but the other became negative and in this case griseofulvin therapy was stopped The remaining 9 patients had some degree of nail dystrophy after one year, with fungus demonstrable in 7 of them but not in the other 2 (table XII)

MYCOLOGICAL CHANGES

Treated and Control Patients

Of the 59 patients with toenail lesions who received griseofulvin for from ten to fifty-two weeks, only 9 became mycologically negative in two consecutive months by direct and culture examinations

These became negative after the following periods of treatment sixteen weeks (1 patient), twenty (1), twenty-four (1) twenty-eight (1), thirty-two (2), and forty (3)

Of the remaining 50 patients, 30 had received griseofulvin for at least twenty-four weeks and were still mycologically positive (6 after twenty-four weeks, 5 after twenty-eight, 2 after thirty-two, 7 after thirty-six, 3 after forty, 5 after forty-four, and 2 after forty-eight)

Of 23 patients with fingernail lesions who were studied mycologically, 7 became mycologically negative in two consecutive monthly examinations by direct and culture methods

They became negative after the following periods of treatment twelve weeks (1 patient), sixteen (2), twenty (1), twenty-four (1), twenty-eight (1), and forty (1)

Of the remaining 16 patients, 8 had completed at least twenty-four weeks' therapy and were still mycologically positive (1 after twenty-four weeks, 4 after twenty-eight, 1 after thirty-six, 1 after forty, and 1 after forty-eight)

Excluding toe-web lesions, the skin lesions of 24 of 60 patients became mycologically negative on two consecutive monthly examinations by the time griseofulvin had been given for eight weeks

Another 7 patients became negative after twelve weeks' treatment, 8 after sixteen, 5 after twenty, 1 after twenty-four, 1 after twenty-eight, 3 after thirty-two, 2 after thirty-six, and 1 after forty 2 of these patients who were apparently cured at eight and twelve weeks showed mycological relapse at twenty-four weeks The skin lesions of 8 patients had still not become mycologically negative after treatment for eight to forty-four weeks (1 after eight, twelve, twenty, twenty-four, and twenty-eight weeks, 2 after forty-four, and 1 after forty-eight) In those cases it was the soles or palms which failed to become negative

Toe-web lesions proved to be more resistant to therapy

44 of the above 60 patients with skin lesions had toe-webs affected, and there were 2 other patients whose skin infection was confined to the toe-webs Of these 46, 22 became negative after griseofulvin treatment for eight to forty weeks (10 after eight weeks, 5 after sixteen, 5 after twenty, 1 after thirty-six, and 1 after forty)

The remaining 24 patients were still mycologically positive after periods of treatment up to forty-eight weeks (1 after eight, 1 after twelve, 2 after sixteen, 1 after twenty, 4 after twenty-four, 3 after twenty-eight, 1 after thirty-two, 2 after forty, 5 after forty-four weeks, and 4 after forty-eight)

Inpatient Group

By the end of three weeks' treatment † in hospital, all

TABLE XII—PRELIMINARY STUDY RESULTS AFTER ONE YEAR IN 11 CASES RECEIVING GRISEOFULVIN

Patient	Fingernails		Toenails	
	Appearance	Mycology	Appearance	Mycology (direct examination)
A*			Normal (from 9 mos)	Negative
B			Normal (from 7 mos)	Positive (sole and toe-webs also positive)
C	Dystrophic	Negative (from 7 mos)	Dystrophic	Positive (toe-webs also positive)
D	Normal (from 7 mos)	Negative	Dystrophic	Positive
E	Slightly dystrophic	Negative (from 7 mos)	Slightly dystrophic	Negative
F	Normal (from 7 mos.)	Negative	Dystrophic	Positive (toe-webs also positive)
G	Normal (from 5 mos)	Negative	Slightly dystrophic	Positive (toe-webs also positive)
H	Normal (from 8 mos)	Negative	Dystrophic	Positive
I	Normal (from 8 mos)	Negative	Dystrophic	Positive
J†			Dystrophic	Negative
K	Normal (from 7 mos)	Negative	Dystrophic	Positive

* Griseofulvin therapy stopped after 9 months
† Griseofulvin therapy stopped after 7 months

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† The first week was spent in making detailed pre-treatment observations

TABLE XIII—MYCOLOGICAL RECORD OF PATIENT C (FEMALE) (T RUBRUM ISOLATED FROM FEET AND HANDS)

Week	Feet						Hand			
	Nails		Webs		Soles		Nails		Palm	
	D	C	D	C	D	C	D	C	D	C
0	+	0	+	3/6	+	0	+	0	+	0
1	+	0	+	11/15	+	2/6	+	0	+	5/9
2	+	0	+	13/17	+	0/12	+	0	+	11/15
3	+	0	+	16/17	+	1/18	+	0	+	2/9
4	+	0	+	0	+	0	+	0	+	0
5	+	0	+	9/12	+	2/12	+	0	+	0/6
6	+	0	+	0/6	+	0/6	+	0		0/6
10	+	0	+	0/6	+	0/6	+	0		0/6
14	+	0	+	2/3		0/6	+	0		0/6
18	+	0	+	0/6		0/6	+	0		0/6
23	+	0	+	0/6		0/6	0	0		0/6
28	+	1/3	+	1/3		0	0	0		0
34	+	0/3	+	0		0		0		0
37	+	0/3	±	0		0		0	0	0
42	+	0/3		0		0		0	0	0
46	+	2/3	+	0/3		0		0	0	0
51	+	0/3	+	0/3		0		0	0	0

D =direct microscopy ± =scanty fragments of mycelium
C =culture 0 =not performed
+ =positive =negative
Fractions Numerator =positive cultures
Denominator=number of specimens taken from patient

11 patients continued to show fungous mycelium in skin scrapings from the sole and toe-webs and in toenails It also persisted in the fingernails of 7 of 7 patients, though negative results were obtained from the palms of 2 of 7 patients who were previously positive 1 patient with facial infection also became negative and his groin lesions showed a significant diminution in fungus

By the twelfth week, positive results on direct examination were still recorded for toenails in 11 of 11 patients examined, for toe-webs in 5 of 8, for soles in 3 of 11, for fingernails in 7 of 8, and for palms in 1 of 5 patients examined

After a year, of the 11 patients studied, 8 still showed fungus in toenails, 3 in toe-webs, and 2 in soles None, however, showed fungus in fingernails or palms While there was a dramatic reduction in the frequency with which fungus could be cultured, it was still grown after six months' treatment from the toenails of 7 patients, the toe-webs of 2, and from the soles of 2 Save in 1 patient whose toenail and sole cultures remained positive (*T rubrum*), cultures were negative, however, where performed after a year Table XIII shows a characteristic mycological case-record

TRICHOPHYTIN TESTS—INPATIENT GROUP

Trichophytin skin tests were carried out by the same person (C J S) on 9 patients before active therapy and after seventeen days and one year of griseofulvin treatment

The same batch of *T rubrum* antigen (Bencard) was used for all tests, an intradermal inoculation of 0 1 ml being administered The diameter of induration produced was recorded, measurements of 5 mm or more appearing within ten minutes (immediate reaction) or in forty-eight to seventy-two hours (delayed reaction) were considered positive providing a control solution gave negative results

The tests produced positive immediate reactions in 7 of the 9 patients tested before treatment and 1 of these became negative after a year's treatment There was an overall reduction in the induration produced in the test at seventeen days compared with the pre-treatment reaction, and a further reduction in all but 3 cases at the end of a year (table XIV) The delayed reactions were negative except in 1 patient who gave a 12 mm reaction before treatment and a 15 mm reaction a year later

TABLE XIV—*TRICHOPHYTIN* REACTIONS RECORDED BEFORE AND DURING GRISEOFULVIN THERAPY

Patient	*Immediate reaction (mm induration)*		
	Before treatment	After 17 days' treatment	After 1 year's treatment
J	+(18 mm)	+(14 mm)	+(6 mm)
C	+(12 mm)	+(10 mm)	+(10 mm)
E	+(15 mm)	+(8 mm)	+(14 mm)
A	+(15 mm)	+(9 mm)	−(0 mm)
H	+(10 mm)	+(8 mm)	+(6 mm)
G	+(10 mm)	+(8 mm)	+(6 mm)
D	+(12 mm)	+(8 mm)	+(10 mm)
K	−(0 mm)	−(0 mm)	−(0 mm)
I	−(3 mm)	−(3 mm)	−(0 mm)

All these patients suffered from *T rubrum* infection except E where the fungus responsible was *T mentagrophytes* var *interdigitale*
+ =positive reaction — =negative reaction.

Discussion

It is clear that griseofulvin is a strikingly effective remedy for this group of chronic ringworm infections The results reported here confirm those reported by Pardo-Castello (1959), Blank and Roth (1959), Goldman (1959), Sulzberger and Baer (1959), Blank et al (1959), and Goldman et al (1960) In retrospect, it is questionable whether an elaborate double-blind trial was necessary for a drug as effective as griseofulvin The results are so striking that even without controls there could be no doubt of its value However, when the trial began, it was by no means obvious that the drug would be so successful, and the trial has provided good evidence of its value soon after its first introduction In addition, the trial has shown that the minor side-effects encountered were as common among the controls as in those given griseofulvin The similarity of incidence of apparently raised monocyte-counts in the control and treated groups is interesting

In the mycological assessment of patients, the finding of fungus either by direct or cultural examination was recorded as positive This procedure was adopted because griseofulvin is a fungistatic and not a fungicidal antibiotic, and because of the known difficulty of growing fungus from infected nails even of untreated patients

Patients showed considerable variation in clinical response to griseofulvin Initial improvement of skin lesions was seen as early as the second week and as late as the twenty-fourth Toe-web lesions were not investigated fully in this study, in view of the multiplicity of causes of maceration and other skin abnormalities at these sites Toe-webs were, however, investigated mycologically, and persistence of fungus was observed in spite of griseofulvin therapy Eight to forty-eight weeks' griseofulvin treatment failed to eradicate infection from toe-webs of 52% of patients harbouring fungus All other skin lesions in the treated group returned to normal clinically after eight to thirty-six weeks' griseofulvin therapy, a few of these remained mycologically positive

Toenails failed to return to normal appearances in 26 of 32 treated patients, 11 of whom had been receiving treatment for forty-four weeks or longer The fate of fingernails was considerably better in that all but 5 of 22 patients showed normal nails after treatment varying from twelve to forty weeks Response to treatment as assessed mycologically was less dramatic than the clinical observations appear to indicate For example, a proportion of affected fingernails which had become clinically normal were still mycologically positive

In most of the 9 patients on whom trichophytin tests were performed, there was an overall diminution in the immediate positive reaction during treatment The immediate response to this antigen is a particular feature of patients infected with *T rubrum* in contrast to those infected with other dermatophytes From these limited observations, a controlled study of larger numbers of subjects would seem worth while

Like other fungistatic agents, griseofulvin does not seem to have any significant value in the topical therapy of *T rubrum* infection However, its efficacy by the oral route represents a major therapeutic advance For the first time, it is now possible, by prolonged treatment, to restore to normal appearances a high proportion of nails of patients with tinea unguium due to *T rubrum*. Unfortunately, as the present study confirms, mycological cure is more difficult to achieve, and the ultimate prognosis, once griseofulvin therapy is stopped, remains to be known

Summary

The strikingly successful results of treatment of chronic ringworm infection with 1.5 grammes daily of orally administered griseofulvin are described

Patients were studied in two ways

1 A controlled trial was carried out to compare a group of patients treated with griseofulvin for four months with a group given an inactive preparation for the same length of time Numbers in this trial were kept to a minimum by using a restricted sequential procedure It was found that 31 out of 33 treated patients showed definite clinical improvement compared to only 1 of 31 control patients Minor side-effects and raised monocyte-counts were as common in control as in treated patients

2 The 33 treated patients continued on griseofulvin for periods ranging from four to twelve months 30 control patients received griseofulvin (after four months as controls) for from two and a half to eight months In addition, 11 other patients have been followed up for one year

The response to therapy varied among patients studied Clinical improvement of skin lesions was noted in most instances by the eighth week. Appearances were usually normal by the sixteenth week and all skin lesions had abated by the thirty-sixth week

Patients with fingernail lesions almost all improved by the twelfth week, but only 62% of patients with toenail lesions showed improvement in this time By the tenth month, 80% of patients with fingernail lesions had normal nails compared with 12% of those with toenail lesions Among the 11 patients followed for one year, 6 of 8 with affected fingernails were normal at the end of a year compared with only 2 of 11 with affected toenails

40% of patients with skin lesions (excluding toe-web lesions) became mycologically negative by the eighth week compared with 22% of those with toe-web infections After eight to forty-eight weeks' treatment 13% of patients with skin lesions still remained positive compared with 70% of those with affected fingernails and 85% with affected toenails Among patients followed for one year, all the 8 with fingernail lesions were negative after a year, but only 3 of 11 with toenail lesions were negative by that time

A diminution in the immediate positive reaction to the trichophytin test was observed during treatment in a limited number of patients

No side-effects attributable to griseofulvin were encountered

It is concluded that griseofulvin is a safe, effective remedy for chronic ringworm infections, but long-term treatment is necessary

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Statistical Appendix

The usual tests of significance of observed differences between two groups of patients in a therapeutic trial assume that the number of patients involved is decided quite independently of the results of the trial The decision to stop a trial and test the significance of any difference is made without previous analysis of the results However, it is often desirable that differences between the groups should be analysed as they become evident so that a trial can be brought to an end as soon as it is clear that one treatment is better than another In order to do this, special statistical methods of sequential analysis have been evolved (Armitage 1954)

Until recently, it was considered that these methods only applied to trials where the response to treatment was seen quickly and where the sequential analysis provided the final test between treatments However, Armitage (1958) has now described a way of using sequential methods in trials where the response is not available for some time after the onset of treatment In such cases, if patients are entering a trial at weekly intervals and results are not seen until some months after entry, then at the moment of stopping new admissions to the trial there will be many patients for whom results are not yet available In this situation sequential analysis is used only to decide when to stop the intake of new patients, and full analysis is carried out on the larger numbers available when the response to treatment of all the patients already in the trial can be assessed This was the method used in the present trial of griseofulvin

The boundaries of the chart were calculated in the following way It was assumed that 300 patients would enter the trial in six months, and that this should be the maximum period for entry It was then postulated that, on the average, treated patients would show definite clinical improvement in three months and control patients would not show definite improvement at all By using a formula given by Armitage (1959), it appeared that, under these conditions, about 80 pairs of patients would have shown a preference (i e, that one member of a pair would be improved, the other not improved) after the trial had been running for six months This number was then referred to table 3 7 of Armitage (1960) where a suitable plan was available with a maximum number of 62 preferences Using this figure of 62 pairs showing preference the parameters of the boundaries of the chart were taken from his table The boundary lines are drawn in such a way that if griseofulvin was ineffective, the outer boundaries ABC or DEF would be reached by chance only once in twenty times a line reaching ABC thus indicates a significant ($P<0.05$) advantage to griseofulvin The degree of advantage tested by this plan is such that if in the long run treated patients improve at least 3 times as quickly as controls, then 95 times in 100 the plotted line will reach ABC If both treated and control patients improve at about the same rate, then 95 times in 100 the line will reach XYZ

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ADRENALECTOMY AND HYPOPHYSECTOMY FOR ADVANCED CANCER OF THE BREAST

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In 1957 some of us (Atkins et al 1957) reported a series of 30 cases of advanced cancer of the breast operated upon by bilateral adrenalectomy with oophorectomy and 30 cases operated upon by hypophysectomy At that time a comparison of these two series favoured hypophysectomy, but the results were not conclusive During the past three years further cases have been treated and we can now compare 79 cases operated upon by adrenalectomy with oophorectomy and 70 cases operated upon by hypophysectomy

The choice of operation has, as before, been made by random selection All the patients have previously undergone a radical mastectomy or have come to us with such widespread dissemination that such a limited procedure was no longer justifiable In our first 60 cases they had exhausted all the possibilities of treatment by local operation, deep X-ray therapy, and hormone therapy We have of course continued to treat operable cancer of the breast by radical mastectomy However, in cases of cancer with dissemination outside the breast and the axillary lymph-nodes, we have introduced certain modifications into the protocol so as to be able to compare cases operated upon relatively early (either by adrenalectomy with oophorectomy or by hypophysectomy) with cases operated on as a last resort, after deep X-ray therapy and hormone therapy have failed 17 patients treated "early" are included in our series of 149, but, as the results of this subsidiary investigation are still inconclusive, we shall not here discuss the merits of early or late operations on the endocrine organs The present series therefore comprises

1 Cases from our previous paper (Atkins et al 1957) 60
2 Cases selected by randomisation for "early" endocrine operation adrenalectomy 10, hypophysectomy 7
3 Cases in which we have exhausted all possibilities of deep X-ray therapy and hormone treatment, and then resorted to a "late" endocrine operation 6
4 Cases which when referred to us had already exhausted deep X-ray therapy and hormone treatment 66

Total = 149 cases

In each of these four groups, randomisation has determined whether bilateral adrenalectomy with oophorectomy or hypophysectomy should be performed Patients operated upon since 1957 have been admitted for final assessment a week before either operation Their medical fitness for surgery is then determined by one of us (K S M), who does not know which procedure the patient is to undergo The surgeon who is to perform the operation therefore has no say in this decision, and so cannot modify his results by refusing bad-risk cases As these patients have little or nothing to lose, operation is advised unless their condition makes the anæsthetic risk prohibitive or unless permanent structural damage is so severe (as in the case of complete cord paralysis) that a major operation seems unwarranted In fact operation has been withheld in only 6 instances (table I) To these a further 3 patients should be added who died while awaiting admission These 9 patients are excluded from the 158 originally allocated, leaving a total of 149, 79 of whom were treated by adrenalectomy and 70 by hypophysectomy

During the first week in hospital the opportunity is taken to investigate the patients fully regarding both the extent of the disease and fitness for operation All lesions are accurately measured and visible ones are photographed, radiographs are taken of the spine, chest, pelvis, femur, and humerus, and films which show obvious metastases are set aside for comparison with those to be taken after operation These measurements are used as the baseline for monthly evaluations of the "mean clinical value" Skull X-rays are obtained on patients selected for hypophysectomy Estimations are made of the hæmoglobin, white-cell, and differential counts, together with the erythrocyte-sedimentation rate and blood-group, the levels of serum cholesterol and alkaline phosphatase are also measured It has also been our practice, since earlier cases have been included in the series, to photograph the patients before operation These photographs can then be used for comparison with pictures taken every six months after operation, so that the extent of facial alteration—particularly the development of myxœdema or the features of Cushing's syndrome—can be noted

TABLE I—CASES DISCARDED FROM SERIES

Patient	Age	Reasons for withholding surgery	Survival time (weeks)
A	60	Complete paraplegia at T4 level	26
B	52	Uræmia	Less than 1
C	45	Hemiplegia and mental change due to cerebral metastases	4
D	33	Severe dyspnœa with pleural effusions	7
E	46	Severe dyspnœa with pulmonary metastases	Less than 1
F	43	Congestive cardiac failure	2

Survival-time is counted from the date of the decision to withhold operation

A total "five-day collection" of urine is taken from each patient and aliquots from this pool are used to measure œstrogens (œstrone, œstriol, and œstradiol-17β), pregnanediol, total 17-oxosteroids, 17-oxogenic steroids, dehydroepiandosterone, androsterone, ætiocholanolone, pooled 11 oxy-17-oxosteroids and gonadotrophins These estimations, made by Dr Bulbrook and Dr Greenwood at the clinicopathological laboratories of the Imperial Cancer Research Fund, are reported in an accompanying paper (Bulbrook et al 1960)

This period in hospital is also utilised for tapping pleural effusions if they are causing symptoms and for transfusing those patients who have low hæmoglobin levels After collection of the urine, administration of cortisone is started and a similar preoperative technique is practised as was described by Atkins et al (1957)

Although the two groups are obtained by randomisation it is necessary at this stage to show that neither group has by chance a preponderance of any particular variable. Table II shows that they are similarly constituted

Treatment

Hypophysectomy

The essential features of hypophysectomy as outlined by Atkins et al (1957) have been followed in all cases, but some modifications have been employed from time to time to facilitate the operation. Thus, whereas the first 30 cases were given cortisone by mouth preoperatively for six days, in subsequent cases cortisone was started with 100 mg in divided doses on the day before operation Otherwise the cortisone regime was unchanged, 300–400 mg being given partly by mouth and partly intramuscularly on the day of operation, and thereafter the dosage was steadily lessened until the maintenance level of 25 mg twice daily by mouth was reached on the eighth postoperative day The other chief change in technique is that the pituitary stalk (infundibulum) is no longer occluded with a clip before it is cut, but is simply steadied with a fine hook and cut at the level of the diaphragma sellæ Like others, we have found that its cut ends bleed very little

Otherwise the removal of the pituitary gland is along the same standard lines A right subfrontal approach to the gland is employed, and after section of the pituitary stalk and incision of the diaphragma sellæ, the gland is teased out of its fossa, sometimes in one piece but generally in fragments, with various-shaped curettes, scoops, and suction tips Generally a pledget of cotton-wool steeped in Zenker's fluid has been inserted into the pituitary fossa for two or three minutes to necrotise any pituitary fragments that remain, and then a plug of "cold-curing" acrylic has been placed in the fossa as a safeguard against reunion of the pituitary stalk with any fragments still remaining This technique was recommended to us by Prof Geoffrey Harris, whose experimental work had shown that after pituitary-stalk section the insertion of an obturator would prevent the physiological functioning of any viable pituitary glandular tissue (Harris 1955)

TABLE II—COMPARISON OF THE TWO GROUPS

—	Adrenalectomy (79 patients)	Hypophysectomy (70 patients)
Age		
Mean	50 years	52 years
Oldest	70 „	73 „
Youngest	27 „	32 „
Married	82% (*65*)	70% (*49*)
Parous	57% (*45*)	51% (*36*)
Lactated	47% (*37*)	46% (*32*)
Menopause		
Pre-	29% (*23*)	33% (*23*)
< 5 years post-	25% (*20*)	24% (*17*)
>10 years post-	13% (*10*)	19% (*13*)
Primary not removed	22% (*17*)	24% (*17*)
Years since onset of disease (mean)	4·2	4·0
Previous hormones		
Œstrogens	28% (*22*)	31% (*22*)
Androgens	54% (*43*)	51% (*36*)
Œstrogens and androgens	5% (*4*)	7% (*5*)
None	13% (*10*)	10% (*7*)
Number responding	23% (*18*)	26% (*18*)
Site of secondaries		
Breast	32% (*25*)	17% (*12*)
Skin	46% (*36*)	51% (*35*)
Glands	61% (*48*)	63% (*44*)
Liver	14% (*11*)	13% (*9*)
Chest	22% (*17*)	34% (*24*)
Bone	65% (*51*)	47% (*40*)
Brain	9% (*7*)	1% (*1*)
Predominant secondary		
Breast	6% (*5*)	4% (*3*)
Skin	14% (*11*)	19% (*13*)
Glands	8% (*6*)	3% (*2*)
Liver	8% (*6*)	7% (*5*)
Chest	9% (*7*)	24% (*17*)
Bone	48% (*38*)	41% (*29*)
Brain	5% (*4*)	1% (*1*)
No predominant secondary	3% (*2*)	

In some of the cases the routine operation was modified. Thus in 23 cases, as troublesome bleeding was encountered from the circular venous sinus after the pituitary had been scooped out, the bleeding was controlled by the implantation of 'Gelfoam', while the instillation of Zenker's fluid was dispensed with In 14 cases no acrylic plate was inserted In most cases the olfactory nerve on the side of operation was sacrificed without the patient being subsequently aware of any subjective disturbance of taste or smell Occasionally both olfactory nerves were damaged, but only 28 patients complained of anosmia in one or both nostrils Again in 6 of our first 30 patients some degree of visual-field defect referable to damage to the optic nerves or chiasm was noted, but in only 1 patient was this troublesome No such defects were observed in subsequent cases In several cases during craniotomy the skull flap was found to be involved in bony metastases, but healing presented no special problem

All our operations were performed under general anæsthesia and in this particular series arterial hypotensive or hypothermic anæsthetic procedures were never used In the light of more recent experience, the marked shrinkage of the brain produced by intravenous injection of urea (80 g) may prove advantageous In no instance was it found necessary to resect a portion of the frontal lobe to gain exposure In 2 cases, with a prefixed chiasm, however, the tuberculum sellæ had to be removed to gain exposure Also in one case the craniotomy had to be reopened because of clot formation compressing the right frontal lobe In only 3 cases did death occur within twenty days of the operation and in 1 of these the cause was bleeding from the brachial artery eroded by an ulcer In only 1 case did hypophysectomy prove technically impossible (Atkins et al 1957) Cerebrospinal rhinorrhœa and meningitis did not occur in any case

In most of our hypophysectomised patients various tests to determine the functional depression of thyroid activity were tried, of which the most usual was the depression of the ^{131}I uptake as tested by the neck/thigh ratio (Dr L Gibbons) Generally this test was performed a month after operation and showed low levels of thyroid activity In our material, tests of depression of the urinary excretion of 17-oxosteroids and of the depression of blood eosinophils have been found unreliable, possibly because we did not like to withdraw cortisone before these tests

Adrenalectomy with Oophorectomy

In our previous communication (Atkins et al 1957) the technique of adrenalectomy was described in detail together with the preoperative and postoperative management This technique has been adhered to, partly because it was found very satisfactory and safe, and partly because we decided not to modify our procedure while it was under investigation It consists in performing the operation in two stages At the first stage the ovaries are removed at laparotomy through a subumbilical incision. The patient is then turned on to her left side and the right adrenal is removed through the bed of the eleventh or twelfth rib, whichever is more convenient Preoperative medication with cortisone, and the postoperative regime, to be described later, are the same with the first and the second stages, on the assumption that the right adrenal may be the only functioning adrenal tissue After seven to ten days the left adrenal gland is removed through a similar posterolateral approach

In 2 cases accessory adrenals about 1–2 mm in diameter have been found In both of them it was certain that the accessory adrenal tissue was not a fragment of the main adrenal gland on that side, which had been fractured during manipulation On several other occasions it was thought that accessory adrenal tissue had been discovered, but this proved to be a fragment of the main gland

Postoperative Mortality

Taking as a criterion death within twenty days of operation, the postoperative mortality in this series of 149 cases has been

TABLE III—POSTOPERATIVE DEATHS (WITHIN 20 DAYS)

Adrenalectomy	No of cases
Carcinomatosis	3
Pulmonary infection or collapse	3
Cerebral abscess	1
Total	7
Hypophysectomy	
Carcinomatosis	1
Acute dilatation of stomach	1
Hæmorrhage (due to erosion of axillary artery)	1
Total	3

7 (9%) for adrenalectomy (79 cases) and 3 (4%) for hypophysectomy (70 cases) The cause of death is shown in table III If those cases are excluded in which death was not obviously attributable to the operation, there remain 3 cases of adrenalectomy dying of pulmonary complications, and 1 case of hypophysectomy dying after acute dilatation of the stomach

Thus it does not seem that the mortality of the two procedures differs very greatly, particularly taking into account the fact that bilateral adrenalectomy entails two operations However, further analysis shows that all the 7 postoperative deaths following adrenalectomy were in the group of 17 patients who had either pleural or lung secondaries, whereas only 1 of the 3 hypophysectomy deaths—the acute dilatation of the stomach—belonged to the group of 25 patients who had secondaries in these sites This observation may mean that in cases with impaired pulmonary function due to secondary carcinoma, adrenalectomy, entailing an abdominal operation and two anæsthetics, is more hazardous than hypophysectomy

Postoperative Therapy

Though patients who have undergone hypophysectomy or adrenalectomy can be maintained in perfect health with steroids, they are exposed to dangers which if not promptly recognised and treated may prove rapidly fatal

The adrenal glands secrete two types of hormones necessary to life—namely, glucocorticoids and mineralocorticoids The former are concerned mainly with carbohydrate metabolism and the body's reaction to stress, while the latter control salt and water metabolism and are responsible for the maintenance of blood-pressure Though production of adrenal hormones, especially mineralocorticoids, may continue after hypophysectomy, the amounts secreted are so small and variable that they are of no practical value, and as regards adrenal replacement therapy hypophysectomised and adrenalectomised patients may be considered together

Cortisone, although mainly a glucocorticoid, has in addition a considerable mineralocorticoid action which makes it the ideal steroid for replacement therapy In normal health the adrenal glands secrete an amount of glucocorticoid equivalent to about 25 mg of cortisone daily, but most of our patients are not in normal health, and to allow for the minor stresses of everyday life we regard a maintance dose of 50 mg (taken as one 25 mg tablet night and morning) as the ideal This amount is unlikely to produce the features of Cushing's syndrome or other side-effects

In normal circumstances the body responds to an abnormal physical stress—e g , from infection, trauma, hæmorrhage, an anæsthetic or an operation—by increasing the production of glucocorticoids After hypophysectomy or adrenalectomy it cannot, of course, do this, and the dose of cortisone must therefore be increased to at least 150 mg daily in these circumstances Failure to appreciate this essential principle of therapy has led to the death of several of these patients High doses should be maintained until the emergency is passed, when the cortisone should gradually be reduced by half a tablet (12 5 mg) daily to the original level, provided the physical condition is satisfactory Infection calls for early and energetic use of antibiotics Vomiting, which may in fact be a sign of cortisone deficiency, is likewise an absolute indication for similar increased dosage, if necessary given by the intramuscular route Intramuscular cortisone acetate is slowly absorbed and does not take effect for twenty-four to thirty-six hours, so, in emergency, hydrocortisone hemisuccinate should be given concurrently in a dose of 1–2 ml (50–100 mg) every eight hours either intravenously or intramuscularly

The mineralocorticoid effect of 50 mg of cortisone will maintain a normal blood-pressure in most patients Occasionally, however, severe hypotension may occur with this dose, and for this reason we used to implant all patients before discharge from hospital with 300 mg of deoxycortone, whose effect lasts at least six months We now prefer to treat such patients with a small oral dose of 9-alpha-fluoro-hydrocortisone ('Fludrone', 0 1–0 2 mg daily) in addition to the maintenance cortisone

With satisfactory maintenance therapy, the patient should have a normal tolerance to drugs and can be given the analgesics, sedatives, or other medicines which her condition demands Œstrogens, however, may have an unpredictable effect upon the carcinoma, and, although hot flushes may prove troublesome after endocrine surgery, œstrogen therapy is contraindicated

Complications after Hypophysectomy

Hypophysectomy is almost always followed, within a few months, by some degree of œdema This is usually shown by gain in weight, associated with lassitude The level of the serum-cholesterol, which rises in hypothyroid states, is a valuable guide to the correct dosage of thyroid extract it should not be allowed to exceed 350 mg per 100 ml Usually 65 mg (gr 1) of thyroid extract daily will maintain good health, although occasionally as much as 200 mg (gr 3) may be required

Because of the risk of postoperative epilepsy, hypophysectomised patients are usually given phenobarbitone 30 mg (gr $^{1}/_{2}$) twice daily for a year, but no patient in this series has had fits after craniotomy

Some degree of diabetes insipidus is very common in these patients Its onset is usually within two weeks of operation, and it tends to disappear spontaneously in two to nine months If it seriously disturbs sleep, treatment with posterior-pituitary extract becomes essential This may be given either by inhalation—40 mg (gr $^{2}/_{3}$) of snuff once to three times in the twenty-four hours—or by intramuscular injection of pitressin tannate in oil (1 ml —5 units) which usually acts for two or three days Though posterior-pituitary extracts occasionally give rise to anaphylactic phenomena, this has not been a problem in our series

All patients who *have undergone adrenalectomy* or hypophysectomy should carry a card giving their maintenance steroid therapy, with *instructions* on increasing this dose if the patient is subjected to infection, operation, or other physical stress

Finally, if the best results are to be achieved, the hospital supervising treatment must establish a close liaison with the family doctor When the patient leaves hospital, we send the doctor a printed sheet dealing with aftercare

Methods of Assessment

The mean clinical value (M C V) has been used throughout our series as a method of assessing the response to therapy In this method each lesion is examined four-weekly after treatment and a mark is given according to whether it has improved in comparison with its initial state (2 marks) or worsened (0 marks) If there is some doubt, or the lesion has remained stationary, 1 mark is scored New lesions are marked 0 The marks are then added together and divided by the number of lesions, to obtain an average, after which the figure is multiplied by 6 to bring it to a less unwieldy number

The effect is to grade each patient at her four-weekly follow-up with some mark between 12, which would indicate that all the lesions were better than they were initially, and 0, which would indicate that all the lesions were worse Intermediate marks between 0 and 6, or between 6 and 12, occur because not all lesions respond to treatment to the same extent or at the same time

Although the M C V has remained our main method of measuring the degree of response to either procedure, certain amendments have been introduced which we believe give greater accuracy These amendments, affecting both populations equally, have not influenced the conclusions except to enable us to reach them more rapidly We had recognised for some time that in certain cases—particularly those with many lesions of the same nature, such as skin nodules—it was possible to alter the final M C V by varying the number of lesions originally selected for comparison Thus a patient who had as one factor bony secondaries in the pelvis which were resolving, and as another factor skin nodules which were getting worse, would have an M C V of

$$\frac{(2+0)}{2}\times 6=6$$

If, however, in the same patient the skin lesions were counted separately and were 5 in number, the M C V would be

$$\frac{(2+0+0+0+0+0)}{6}\times 6=2.$$

To overcome this difficulty we now divide all the lesions into various systems, such as skeletal, lymphatic, and cutaneous, and calculate the M C V separately for each system The final mark is then derived by averaging out the marks obtained from each system and the problem of plurality of lesions is largely allowed for

Total M C V During Survival

A comparison of the values of M C V at a fixed period after treatment may be less informative than a comparison which takes into account the general levels of M C V attained throughout the period of survival For each patient, therefore, we calculated the *total* M C V monthly throughout survival A score of 6 was included for the preoperative condition, and any monthly readings which were missing were estimated by interpolation The resulting total is very nearly equal to the area under the curve joining the M C V values for an individual patient Comparison of the means of the total M C V s for the two groups is therefore the appropriate way to test whether the areas under the two summary curves (fig 1) differ significantly

TABLE IV—COMPARISON OF RESULTS FOR THE TWO TREATMENT GROUPS

—	Adrenalectomy		Hypophysectomy		Difference between means ± standard error	S.E diff (t)
	No of patients	Mean value	No of patients	Mean value		
Mean clinical value						
At 3 months	79	5 16	70	6 95	1 79 ±0 76	2 35†
At 6 months	72	4 52	66	6 18	1 66 ±0 87	1 89
At 1 year	70*	2 91	61*	4 34	1 43 ±0 85	1 68
Log (total M C.V)	79	1 548	70	1 769	0 221 ±0 098	2 26‡
Average M.C.V	79	5·48	70	6 57	1 09 ±0·48	2 28‡
Survival (by life-table)						
Proportion surviving						
At 3 months		0 666		0 812	0 146 ±0 071	2·05§
At 6 months		0 596		0 678	0 082 ±0 080	1·02
At 1 year		0·405		0 567	0 162 ±0 084	1 92
Expectation of life (months)		14 2		20 3	6 1 ±3 6	1 70

* Nine patients in each category were followed up for less than a year

Significance of differences

† 0 01 < P < 0 02

‡ 0 02 < P < 0 03

§ 0 04 < P < 0 05

Since individual values of total M C V are distributed in a highly asymmetrical manner, the logarithm was taken of each total M C V The mean value of the log (total M C V) was calculated for each group, and these two means were compared by a *t* test

The total M C V for an individual is influenced both by the length of survival and by the average score during survival It may be relevant to examine the latter feature separately, and the *average* M C V during survival was accordingly calculated for each patient No logarithmic transformation was necessary, since the values of the average M C V are fairly symmetrically distributed The mean values of average M C V in the two groups were compared by a *t* test

Life-tables for Length of Survival

Comparison of the proportions of patients surviving for long periods after treatment is hampered because many patients, still surviving, have not yet been observed for the requisite length of time To ignore the observations on these patients is wasteful, because they contribute information about the survival experience at shorter times after treatment The appropriate technique is the life-table (see, for instance, Merrell and Shulman 1955), in which the probability of survival throughout each consecutive time-interval, is estimated from those patients still alive when it began In the present analysis the successive time-intervals were taken to be one month in length

The life-table provides an estimate of the proportion of subjects surviving to a given time after treatment. The proportions of survivors at three months and six months, in the two groups, were compared by use of Greenwood's (1926) formula for the standard errors The expectation of life after treatment was calculated for each group, and the two values compared by use of Irwin's (1949) formula for the standard errors

Analysis of Results

Main Comparison of Two Treatment Groups

Table IV compares the two groups with respect to various criteria of response The most sensitive comparison of the M C V appears to be at three months, when the difference (in favour of hypophysectomy) is significant well beyond the 5% level A similar degree of significance is attained by the comparisons of log (total M C V) and of the average M C V during survival

The proportions surviving at various times after treatment, estimated by the life-table method, are shown in fig 2 The comparisons in table IV show that the proportions of survivors at three months after treatment differ significantly at the 5% level The differences in the proportions of

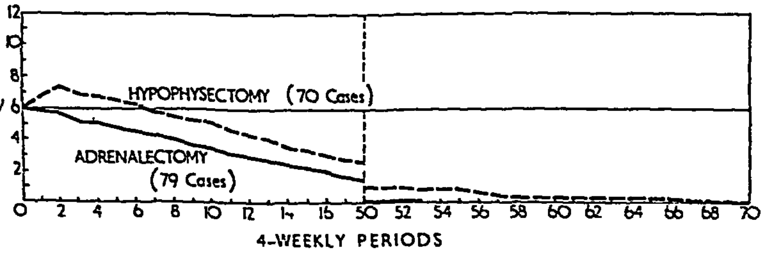

Fig 1—Average "mean clinical value" (4-weekly records) of all adrenalectomy and hypophysectomy cases

et al (1960) indicate that they are not The difference in the accuracy with which the patient's response to operation can be predicted may also indicate a difference between the operations

When the assay results were examined separately for the adrenalectomised and the hypophysectomised patients, the androsterone levels were found to show the same trend as the ætiocholanolone levels—i e, they were highest in the remission groups If the androsterone levels are used for prognosis for hypophysectomy, the results are not as good as when ætiocholanolone alone is considered (in fact, the response of 1 extra patient is incorrectly forecast) For adrenalectomy, however, use of the androsterone levels somewhat improves prognosis, since it would permit correct prediction in 3 of the 6 cases where an incorrect forecast was made on the basis of the original discriminant

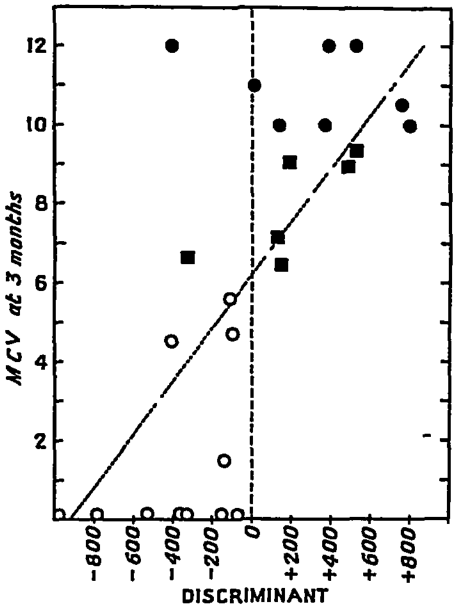

Fig 3—Correlation between the M C V 3 months after hypophysectomy and the discriminant

The broken line running from left to right across the figure is the calculated regression line The correlation coefficient (r)=0 71 ($P<0\ 001$)

● =Patients classified in remission group

■ = „ „ „ intermediate group

○ = „ „ „ failure group

On the other hand, the numbers in the adrenalectomy or hypophysectomy groups are small, and the improvement in prognosis that might come from using either androsterone or ætiocholanolone levels may be more apparent than real A larger series might show that assays of either, or both, of these steroids would be equally useful It seems unlikely that ætiocholanolone assays are more useful than androsterone assays for predicting the response to hypophysectomy, and vice versa for adrenalectomy, but more data are required

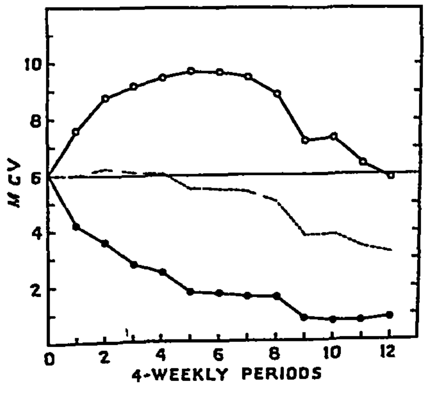

Fig 4—Calculated effect of selection of patients for hypophysectomy on clin[illegible] se of the disease

The [illegible] the [illegible] for all hypophysectomised patie[illegible] e M C V. of patients with posi[illegible] the average M[illegible]

The dehydroepiandrosterone and pooled 11-oxy 17-oxosteroid levels do not seem to have predictive value

The effect of the menopause and of previous hormone therapy on the excretion of endogenous hormones was described by Hayward et al (1959), and apparently no improvement in prognosis can be obtained by taking these factors into account The oestrogens, pregnanediol, and gonadotrophins are most affected by these factors and this may explain why assays of these hormones have been of no prognostic value in this series

Discussion

The above results show that the response of metastatic breast cancer to adrenalectomy or hypophysectomy can be predicted to a great extent from certain measurements of the hormone environment in which the tumour is growing The urinary levels of 17-OHCS and ætiocholanolone are two indices of this environment which are of value

As a practical means of selecting patients for hypophysectomy, the discriminant derived from the 17-OHCS and ætiocholanolone levels appears potentially useful If the patients in the present series had actually been selected on the basis of their discriminants, 13 of the 25 submitted to hypophysectomy would not have been treated in this way Of the 13 rejected, 1 would have been denied remission of the disease, 1 could have had a marginal response, and the other 11 would have failed to respond Although percentages may be misleading with such small numbers of patients, these figures indicate that 85% of those rejected would have failed to respond to hypophysectomy

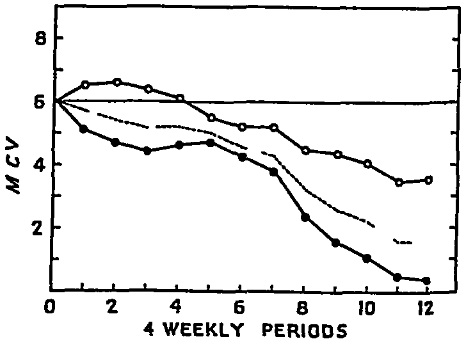

Fig 5—Calculated effect of selection of patients for adrenalectomy on clinical course of the disease

The dotted line shows the average M C V for all adrenalectomised patients The upper line (—○—) shows the M C V of patients with positive discriminants The lower line (—●—) shows the average M C V of patients with negative discriminants

Of the 12 patients who would have been selected for hypophysectomy, 7 (60%) would have obtained remission, while the other 5 would have had a marginal response It must be remembered that in this series we have defined remission so strictly that the overall rate for patients subjected to hypophysectomy is only 32% A remission rate of 60% would be a very substantial improvement

If the mean M C V curve for hypophysectomy patients having a positive discriminant is compared with that of hypophysectomy patients with a negative discriminant, the difference in the clinical course is very striking (fig 4) These results are, of course, retrospective, and a clinical trial would be needed to substantiate them

The discriminant does not seem to be so useful a means of selection in adrenalectomy Admittedly, all patients who in fact had an objective remission would have been treated, but a high proportion of those selected for treatment would have failed to benefit Of 13 patients selected, 6 would have obtained remission, 1 would have been in the intermediate group, and 6 would have failed to benefit. Although selection is not as effective as in the hypophysectomy series, an overall regression-rate of 46% would have been obtained

Fig 5 shows that when the average M C V curve for all adrenalectomy patients with a positive discriminant is compared with the M C V curve for adrenalectomy patients with a negative discriminant, prognosis would not improve the clinical results to the same extent as in hypophysectomy

Atkins et al (1960) have found that in randomly selected patients hypophysectomy is a better treatment than adrenalectomy From this it follows that some of the patients in our intermediate or failure groups would have obtained remission if they had been treated by hypophysectomy rather than adrenalectomy It is possible that these cases might have been those in the adrenalectomy series who failed to benefit in spite of a positive discriminant In other words, as there is a clinical difference in response, the presence of some cases of failed adrenalectomy having a positive discriminant would be expected

The physiological significance of the results of our hormone assays is obscure Judging by the effects of hormones on the growth of the normal breast in laboratory animals, one might expect that prognosis would be related to the levels of œstrogens, progestins, prolactin, and growth hormone The finding that the 11-deoxy-17-oxosteroids (ætiocholanolone in particular), probably largely derived from adrenal dehydroepiandrosterone, and the 17-OHCS, largely derived from cortisol, have predictive value, is unexpected Very probably these two groups of hormones are merely indices of a particular hormone environment of considerable complexity, and determinations of other blood or urinary hormones might provide much more information about this environment

Our results agree very closely with those of Allen, Hayward, and Merivale (1957), when the differences in the methods are taken into account These authors described a correlation between prognosis and the ratio of the 11-deoxy-17-oxosteroids to the 11-oxy compounds However, Plantin et al (1958) and Hobkirk and Forrest (1957) did not find assays of fractionated 17-oxosteroids useful for prognosis in their cases

Several other reports indicate that differences in urinary hormone levels may be associated with differences in response to therapy Huggins and Dao (1954) found that a high œstrogen level after oophorectomy was associated with successful response to adrenalectomy Loraine et al (1957) showed that, in general, postmenopausal women with a high gonadotrophin level are less likely to benefit from stilbœstrol than those with lower levels of excretion These findings emphasise the fact that the hormonal status of the host is of great importance in determining response to endocrine treatment

Summary

The response of metastatic breast cancer to adrenalectomy or hypophysectomy largely depends on the hormonal environment in which the tumour is growing Of the hormonal factors measured in this series of 59 patients the levels of ætiocholanolone and the 17-hydroxycorticosteroids are of most use in predicting the outcome of the two operations They were particularly valuable in indicating the probable response to hypophysectomy

We should like to thank Mr Hedley Atkins and Dr Kenneth MacLean of Guy s Hospital and Mr Murray Falconer and Mr Peter Shurr of the Guy's-Maudsley Neurosurgical Unit, for permission to investigate their patients We are very grateful to Dr P Armitage for his assistance with some of the statistical problems of this work and to Dr C C Spicer for calculating the discriminant function We should also like to thank Miss Y A Leon, Mr B S Thomas, and Mr W G Hunter for their assistance with the hormone assays

Appendix

Statistical Note by DR C. C. SPICER

The constants of the discriminant function were calculated using the combined sums of squares and products "within groups" for the successful, intermediate, and failure patients The significance was then tested by the F test for the generalised distance given by Roy and Bose (1940) The value of F is 5 1 on 2 and 33 degrees of freedom and is significant at about the 0 01 level The constants of the function were rounded to convenient numbers as no great accuracy was justifiable

As regards the general validity of the discriminant its continued success when used on observations other than those from which it was calculated is probably a better justification than a formal test of significance.

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DIAGNOSIS OF POLYMYOSITIS

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DERMATOMYOSITIS was defined by Steiner in 1905 as an acute, subacute, or chronic disease of unknown origin characterised by dermatitis and multiple foci of muscle inflammation and œdema Polymyositis has long been recognised as the same disease process in which the skin changes are slight or absent The disease, which has received comparatively little attention in this country (see Bauwens 1956, Nattrass 1956, Richardson 1956, Walton 1956, Walton and Adams 1958), is still little known here and is certainly commoner than has been previously thought We have discovered 28 cases of the disease in ten years at one London teaching hospital

The mode of presentation varies according to the patients' ages and at all ages polymyositis may mimic other general medical and neurological disorders In some cases the diagnosis cannot be made with certainty, for muscle biopsy may be normal, the electrical findings misleading and the clinical picture atypical Fortunately two of these three diagnostic features are usually positive.

Material and Methods

We describe here our experience of the 28 cases (see accompanying table)

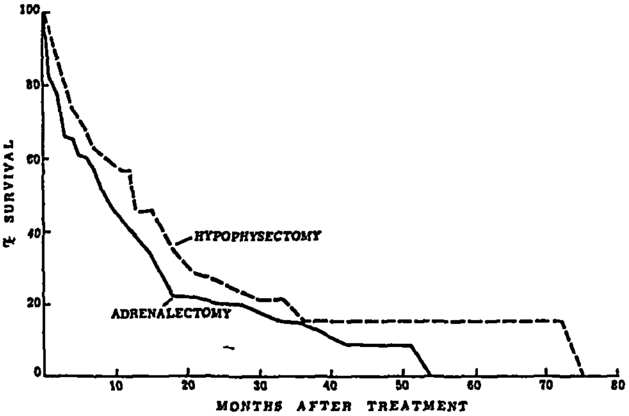

Fig 2—Proportions of survivors at 4-weekly intervals after treatment, calculated by the life-table method

survivors at one year and in the expectations of life are substantial, but are technically rather less significant

The operative mortality in the adrenalectomy group was higher than in the hypophysectomy group, but table V shows that the general advantage of hypophysectomy is not due solely to this difference, there is also a substantial difference in the proportions of deaths between twenty-one days and three months after surgery Table VI shows two comparisons of the M C V for those patients who survived the initial period of 0–20 days The mean values of M C V at three months differ significantly at the 5% level, and the mean values of log (total M C V) very nearly do so

TABLE V—COMPARISON OF MORTALITY IN THE TWO GROUPS FOR DIFFERENT PERIODS AFTER THE START OF OPERATION

—	No of patients	No of deaths		
		0–20 days	21 days–3 months	0–3 months
Adrenalectomy	79	7	19	26
Hypophysectomy	70	3	10	13

The M C V at Three Months

The most sensitive method of comparing the two groups seems to be provided by the M C V at three months, and the further analyses were accordingly performed with this criterion of response rather than with the others considered above

These analyses were designed to show whether the M C V at three months was related to any of the characteristics of the patients which had been recorded on entry to the trial Any evidence as to which factors affect prognosis is intrinsically interesting, but it also has a bearing on the main comparisons between the two treatments The discovery of such factors may not only allow reduction in the random errors associated with the comparisons but also enable some correction to be made to the comparison if the patients allocated to the two groups happen to differ appreciably, on the average, for the factor under consideration

TABLE VI—COMPARISON OF RESULTS FOR PATIENTS SURVIVING 20 DAYS FROM START OF OPERATION

—	Adrenalectomy		Hypophysectomy		Difference between means ± standard error	S E diff (t)
	No of patients	Mean value	No of patients	Mean value		
M C.V at 3 months	72	5 67	67	7 27	1 60 ±0 73	2 19*
Log (total M C.V)	72	1 621	67	1 812	0 191 ±0 097	1 97

* 0 04<P<0·05

Various factors such as age, marital status, relation to the menopause, effect of removal of the primary tumour, response to previous hormone therapy, the number of secondary sites, and the effect of time since the onset of the disease were all examined in this way For each factor a statistical analysis was carried out to show whether (*a*) the difference between the values of the mean M C V for the two groups differed significantly from one category to another, and (*b*) whether the general level of the M C V , taking both treatment groups together, varied from one category to another With two exceptions, the differences shown by these analyses were not significant at the 5% level

One exception was the effect of the duration of preoperative symptoms The increase in M C V with increasing time since onset is significant at the 5% level

As it happened, rather more patients in the adrenalectomy group than in the hypophysectomy group had a time since onset of under two years, and this would tend to put the adrenalectomy group at a disadvantage This effect can be *overcome by comparing the means within each of the three* categories of time since onset These differences, with their standard errors, are given in table VII They do not vary significantly among themselves and their weighted mean is 1 66±0 75, which is significant at the 5% level The disproportionate distribution of time since onset, then, has not appreciably affected the main conclusion

TABLE VII—EFFECT OF TIME SINCE ONSET ON THE M.C V AT 3 MONTHS

Years	Adrenalectomy		Hypophysectomy		Difference between means ±S.E.
	No of patients	Mean M C V	No of patients	Mean M C.V	
0–	19	2 81	11	5 96	3 15±1 73
2–	35	5 79	39	6 54	0 75±1·06
5–	25	6 08	20	8 31	2 23±1 37
Total	79		70		

Weighted mean of differences
1 66±0 75
(0 02<P<0 03)

The other factor to show a significant relation with M C V was the removal of the primary tumour (table VIII) The difference between the mean M C V s for the two treatments is particularly marked in the group of patients who had not had the primary tumour removed The weighted mean of the differences is 1 84± 0 75, which is significant well beyond the 5% level

TABLE VIII—EFFECT OF REMOVAL OF THE PRIMARY TUMOUR ON THE *M C V AT 3 MONTHS*

Primary tumour	Adrenalectomy		Hypophysectomy		Difference between means ± S.E.
	No of patients	Mean M C V	No of patients	Mean M C V	
Not removed	17	2 30	17	6 71	4·41±1·56
Removed	62	5 95	53	7 03	1·03±0·85

Weighted mean of differences
1 84±0 75
(0 01<P<0 02)

The number of secondary sites shows an effect in the expected direction, although the trend is not sufficiently pronounced to reach the customary levels of significance

What is somewhat surprising, in view of previous reports, is that in our series the response to previous hormone therapy seems to give no indication as to whether operation will be successful or not (table IX)

Practical and Scientific Issues

The above analysis demonstrates quite clearly that, in advanced cancer of the breast, hypophysectomy has a more

TABLE IX—EFFECT OF PREVIOUS USE OF AND RESPONSE TO HORMONE TREATMENT ON THE M C.V AT 3 MONTHS

—	Adrenalectomy		Hypophysectomy	
	No of patients	Mean M C.V	No of patients	Mean M C.V
Hormones not used	10	4 65	7	6·40
Hormones used				
No response	49	4 83	45	7 08
Response to œstrogens	9	7 20	7	4 67
Response to androgens	9	5 57	11	8 23
Unknown	2		0	
Total	79		70	

favourable effect than bilateral adrenalectomy with oophorectomy This difference is revealed both by an analysis of the survival-rates and by the mean clinical values In both types of analysis the superiority of hypophysectomy has been established well within the limits of statistical acceptability Further comment, however, is necessary on the implications of this finding

In the first place the two populations compared are heterogeneous (Atkins 1960) That is, they are made up of individuals of different manifestations of the disease cancer of the breast Randomisation will have ensured as far as possible that these elements of the heterogeneity are evenly distributed between the contrasted populations, but it will not, of course, have eliminated them within the populations What we have shown is that, taking one of these heterogenous populations as a whole and comparing it with another heterogeneous population, hypophysectomy was better than adrenalectomy What we have got to be careful about is that there is not, hidden away within this conglomerate, an age-group or a manifestation which would be better treated by adrenalectomy, or, conversely, one that is overwhelmingly better treated by hypophysectomy If we compared this situation with an imaginary controlled clinical trial on the effect of œstrogens we should probably find that a heterogeneous population of cases of advanced cancer of the breast treated with œstrogens did better than a control group given a placebo Such a result might well emerge because the majority of the population was well past the menopause, and the beneficial effect of œstrogens on this group would disguise its harmful effect on the younger patients who were in the minority

Exceptions to the general rule might be found among the different manifestations liver secondaries might be found to behave differently from bone secondaries, and so on The only way to resolve this difficulty is to continue the trial until there are enough cases in the different categories to be able to make a detailed appraisal of each of these We may well ask whether, having shown that one method is on the average superior to the other, it is ethical to continue such a trial

We have shown that hypophysectomy is better than adrenalectomy with oophorectomy, and this difference is significant well within the 5% level of acceptability However significant the difference is, we may ask ourselves, nevertheless, the equally important question—how big is this difference? Is this difference so great that it must determine policy?

We get some idea of the degree of difference in effect between hypophysectomy and adrenalectomy with oophorectomy by the figures 20 3/14 2, being the expectation of life in months after operation, and 6 57/5 48, being the average M C V during survival, after the two operations respectively Does this imply that we must discard adrenalectomy with oophorectomy and subject these patients to hypophysectomy? About 8000 women die from cancer of the breast in England and Wales each year We may assume that about 7000 of these come within the category of patients for whom one or other of these operations might, at some time, be helpful Apart from anything else therefore, the magnitude of the problem makes it impracticable to turn all such patients over to the neurosurgeon for hypophysectomy and to discard adrenalectomy which has been shown to be only a little less effective Furthermore, the performance of 7000 hypophysectomies a year is beyond the capacity of the facilities in this country It is true that the work of Bulbrook, Greenwood, and Hayward (1960) on the urinary steroids will make it possible to avoid operating upon those patients for whom the chance of benefit is slight, and this will scale down the problem

From the cases at our disposal we have not been able to detect any characteristics in the patient which make hypophysectomy the undoubted operation of choice We do, however, believe that patients with pulmonary metastases causing dyspnœa should not be submitted to two abdominal operations Our future policy, therefore, will be not to treat such cases by adrenalectomy With the remainder the situation is, unfortunately, not so simple Even with the exceptional neurosurgical facilities at our disposal, and the preselection which will in future be possible (Bulbrook, Greenwood, and Hayward 1960), hypophysectomy for all the patients would mean a considerable delay for many before the operation could be performed In deteriorating cases this delay might well offset—or more than offset—the slight advantage that this operation enjoys over adrenalectomy with oophorectomy In the circumstances we cannot escape the problem of selecting some proportion of the cases for immediate hypophysectomy, and apart from the patients with secondaries in the chest, we have no evidence upon which to select that proportion Hence we think it ethical to continue to make that selection on a random basis until such time as further experience enables us to define the circumstances in which hypophysectomy is certainly the operation of choice

If, then, our results show that the difference between these forms of treatment is significant but limited, what is their value? Although in the prevailing circumstances this difference is not great enough to dictate a change of policy, the fact that there *is* a difference is an important finding It may be that hypophysectomy is the more complete operation, and that after adrenalectomy some secreting tissue is left behind—not necessarily locally, but still under pituitary control The difference might, on the other hand, indicate that the pituitary gland has an influence on the breast cancer cell which is different from and stronger than that of the adrenal glands, thus focusing the need for research on, for instance, the growth hormone and other hormones peculiar to the pituitary gland, and also on other methods of pituitary destruction or inhibition—eg , by radioactive isotopes or anti-hormones

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SELECTION OF BREAST-CANCER PATIENTS FOR ADRENALECTOMY OR HYPOPHYSECTOMY BY DETERMINATION OF URINARY 17-HYDROXYCORTICOSTEROIDS AND ÆTIOCHOLANOLONE

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IN recent years adrenalectomy with oophorectomy, or hypophysectomy, have been used as the last effective treatment for metastatic breast cancer, and about half of the patients thus treated receive some benefit If the result of the operation could be predicted, unnecessary major surgery would be avoided for those patients who obtain no remission Hitherto no method of prediction has been found clinically useful

We report here an attempt to predict the response by determining urinary œstrogens, pregnanediol, total and fractionated 17-oxosteroids, 17-hydroxycorticosteroids, and gonadotrophins before operation This was done in 65 cases, randomly selected for either operation A preliminary account of this work has already been given (Hayward, Bulbrook, and Greenwood 1959)

Methods

Chemical

Five consecutive twenty-four-hour specimens of urine were collected from each patient in the week before operation

During collection the urine was stored at 4°C, the five specimens were pooled, and the urine then stored at −20°C unless the analyses were to be carried out immediately No laxatives were given, drugs were restricted as much as possible, and, if any hormones had been administered, at least a week was allowed to pass between the last dose and the first day of the urine collection Preoperative cortisone was not administered until the collection was complete In premenopausal women an attempt was made to collect the urine between the seventeenth and the twenty-fourth day of the menstrual cycle, but accurate timing was not always possible, because some of the patients had cycles of varying length and of irregular occurence

Total 17-oxosteroids and 17-hydroxycorticosteroids (17-OHCS) were assayed as described by Appleby et al (1955) except that the bismuthate oxidation lasted one hour Dehydroepiandrosterone, androsterone, ætiocholanolone, and the 11-oxygenated 17-oxosteroids were determined by the method of Kellie and Wade (1957) and the purity of each fraction was checked by paper chromotography The dehydroepiandrosterone results are generally overestimates, owing to the presence of other Zimmerman-reacting compounds in this fraction The 11-oxygenated 17-oxosteroids were measured as a group since routine separation proved impossible The 11-deoxy compounds were measured against their own standards, but the levels of 11-oxy compounds were assayed in terms of standard dehydroepiandrosterone Pregnanediol was measured by the method of Klopper, Michie and Brown (1955) Gonadotrophins were assayed by the method of Loraine and Brown (1959) Urinary œstrone, œstradiol-17β, and œstriol were determined by the method of Brown (1955) as modified by Brown, Bulbrook, and Greenwood (1957)

The Patients

The data for 6 of the 65 patients were eventually discarded—in 2 cases because diabetes insipidus made it impossible to carry out the hormone assays, in 1 because of metastases in the pituitary gland and in a 4th because a decompression was done with hypophysectomy and it was impossible to tell whether benefit resulted from relief of raised intracranial pressure or from removal of the pituitary gland In 2 further cases some of the hormone assays were not completed

Of the 59 remaining patients, 13 had been previously treated with œstrogens and 29 with androgens, while the remainder had had no hormones 25 were premenopausal, though in most of these menstruation had ceased because of recent hormone administration

Clinical Evaluation of Response to Treatment

A complete clinical assessment was made during the week before operation, as described in the accompanying paper (Atkins et al 1960) After operation the patients were examined four-weekly On the basis of the clinical findings, and before the urinary hormone levels were made known, they were graded into three groups

1 *Remission* —All visible and palpable lesions regressed

2 *Intermediate*—This group contains (a) cases in which the disease remained almost stationary and (b) those in which regression was incomplete or shortlived

3 *Failure*—The disease was apparently unaffected by treatment

The numbers in these groups were

(1) Remission	14 cases (24%)
(2) Intermediate	18 cases (30%)
(3) Failure	27 cases (46%)

It will be noted that the remission-rate of 24% is much lower than that usually given for series of this kind This reflects the design of the experiment, in that we were trying to find an accurate method of prognosis by comparing the clinical and the hormone-assay data If one half of the experiment, the clinical half, contained inaccuracies, this might well conceal any trend in the other half For this reason cases were allotted to groups 1 and 3 only if their clinical response was absolutely certain

Mean Clinical Value

Atkins et al (1960) have compared the clinical results of adrenalectomy and hypophysectomy using the " mean clinical value " (M C V) In their hands, the M C V three months after operation was the most sensitive factor for comparison We too have used the M C V at three months as an index, since in this way some idea of the gradation of response may be obtained

Results

A preliminary investigation (Hayward et al 1960) suggested that, of the eleven compounds (or groups of compounds) determined, only the 17-OHCS and the ætiocholanolone levels might be of use in predicting the response to adrenalectomy or hypophysectomy However, the results of assays of other hormones will also be mentioned below

The mean 17-OHCS level proved to be higher, and the mean ætiocholanolone level lower, in the failure group than in the remission group The differences between the means are only marginally significant ($p \simeq$ 0 05–0 01) and the overlap between individual values in the two groups *is so large that neither* the 17-OHCS nor the ætiocholanolone levels could be used alone for prognostic purposes However, since the 17-OHCS levels are generally higher and the ætiocholanolone levels lower in the failure group, the difference will be greater when the values are expressed as a ratio The 17-OHCS and ætiocholanolone levels for each patient, and the ratio between them, are

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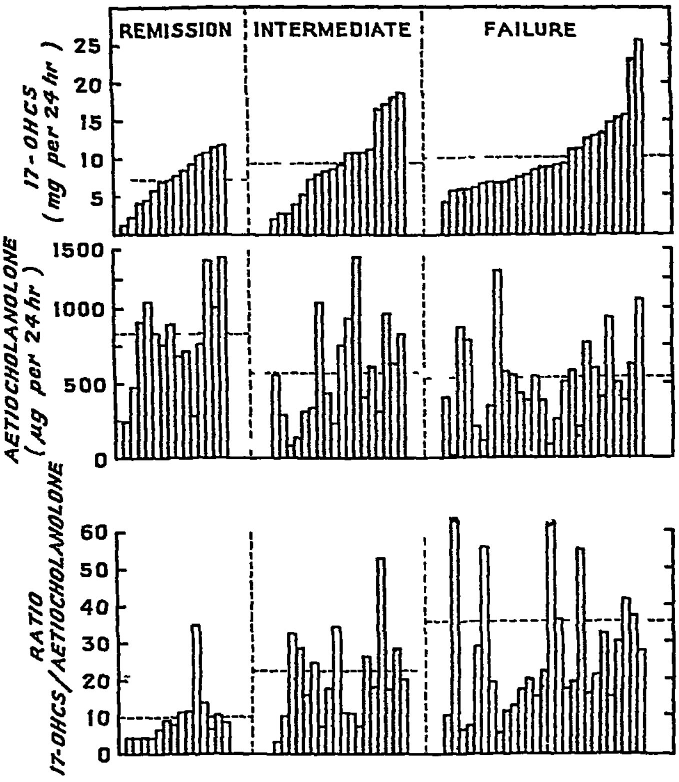

Fig 1—Levels of 17-OHCS, ætiocholanolone, and the ratio between these compounds, compared with response to operation

The vertical columns show the excretion of 17-OHCS and ætiocholanolone and the ratio between them, for each patient in the series (Clear columns, hypophysectomy, stippled columns, adrenalectomy) The 17-OHCS are ranked in order of increasing magnitude and the corresponding ætiocholanolone value, and ratio, are plotted directly below

shown in fig 1 From these levels a simple formula known as a discriminant function (cf Fisher 1952) can be calculated which conveniently expresses the differences in the excretion of these hormones by patients in the remission and the failure group (see appendix)

In the present series this is

80−80 [17-OHCS (mg per 24 hours)] + ætiocholanolone (µg per 24 hours)

Values of this function equal to zero are about equally likely to be found in successful and unsuccessful cases Positive values are more likely to be associated with a successful response to treatment and negative ones with no benefit The constants of this function were originally extracted from the data on the first 41 patients (Hayward et al 1959) Of these 41 cases, 36 are included in the present study and in fig 2 the discriminant is compared with the actual clinical result of the operation Since the first publication an additional 23 patients have been investigated A new discriminant has not been calculated for the present series (which now totals 59 cases), since the new cases have been used to check the validity of the original discriminant These results are also shown in fig 2, from which it can be seen that the original calculation holds for the new cases

When adrenalectomy and hypophysectomy are considered together, it can be seen from fig 2 that, had the discriminant been used for prognosis, the forecast would have been correct in 13 out of the 14 cases which had an objective remission Only 1 patient with a negative discriminant actually benefited from treatment

In the intermediate group of patients, 6 had positive discriminants and 12 negative ones The distribution in this group is curious in that 5 of the 6 patients afterwards submitted to hypophysectomy had positive discriminants whereas 11 of the 12 who were adrenalectomised had negative discriminants

In the failure group, prognosis would have been correct in all the 11 hypophysectomised patients but in only 10 of the 16 adrenalectomised patients

Examination of fig 2 leaves little doubt that the discriminant would have been more useful for predicting the results of hypophysectomy than of adrenalectomy The same difference is apparent if the M C V at three months is used as an index of response (rather than the classification of patients into one of three clinical groups) When the M C V at three months is plotted against the discriminant, calculated from the 17-OHCS and ætiocholanolone assays, a highly significant relationship is found for patients in the hypophysectomy series (fig 3) in other words, the degree of remission obtained from hypophysectomy may be proportional to the ratio of the amounts of urinary 17-OHCS and ætiocholanolone When a similar correlation is attempted for adrenalectomy patients no significant relationship can be demonstrated This is largely because 6 patients with a positive discriminant (who might therefore have been expected to benefit from treatment) failed to obtain regression of the disease after operation The correlation coefficient (r) is 0 25 ($P > 0\ 1$)

Other Hormone Assays

The discriminant was originally calculated on the assumption that adrenalectomy and hypophysectomy are equivalent operations, but the clinical results of Atkins

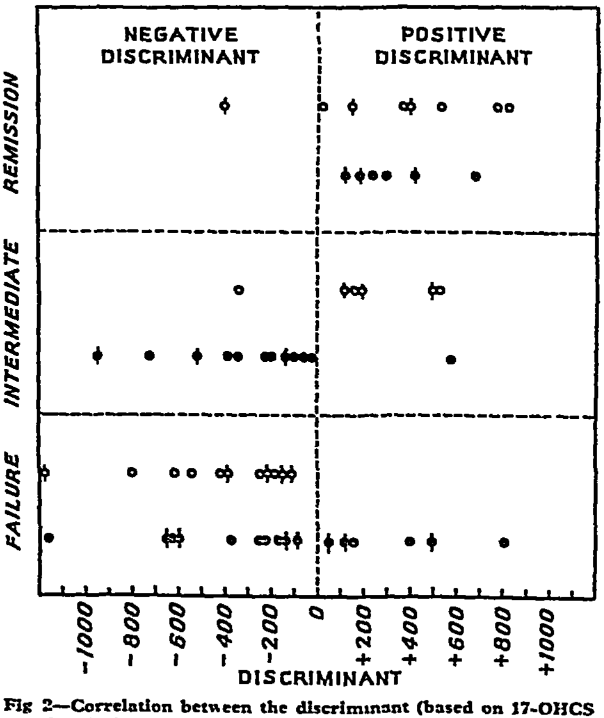

Fig 2—Correlation between the discriminant (based on 17-OHCS and ætiocholanolone levels) and the actual clinical result of adrenalectomy or hypophysectomy

Clear circles, hypophysectomy, black circles, adrenalectomy The discriminant was calculated from data on the cases plotted without vertical lines through the points The new series (see text) are shown as circles with vertical lines through them et al. (1960) indicate that they are not. The difference in the accuracy with which the patient's response to operation can be predicted may also indicate a difference between the operations.

When the assay results were examined separately for the adrenalectomised and the hypophysectomised patients, the androsterone levels were found to show the same trend as the ætiocholanolone levels—i.e., they were highest in the remission groups. If the androsterone levels are used for prognosis for hypophysectomy, the results are not as good as when ætiocholanolone alone is considered (in fact, the response of 1 extra patient is incorrectly forecast). For adrenalectomy, however, use of the androsterone levels somewhat improves prognosis, since it would permit correct prediction in 3 of the 6 cases where an incorrect forecast was made on the basis of the original discriminant.

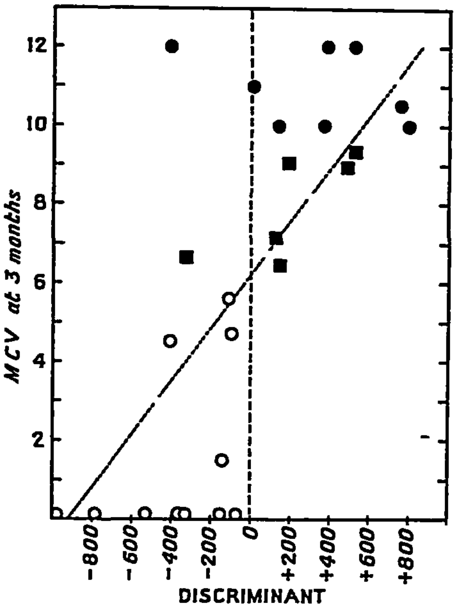

Fig. 3—Correlation between the M.C.V. 3 months after hypophysectomy and the discriminant.

The broken line running from left to right across the figure is the calculated regression line. The correlation coefficient (r)=0.71 (P<0.001).

● = Patients classified in remission group
■ = „ „ „ intermediate group
○ = „ „ „ failure group

On the other hand, the numbers in the adrenalectomy or hypophysectomy groups are small, and the improvement in prognosis that might come from using either androsterone or ætiocholanolone levels may be more apparent than real. A larger series might show that assays of either, or both, of these steroids would be equally useful. It seems unlikely that ætiocholanolone assays are more useful than androsterone assays for predicting the response to hypophysectomy, and vice versa for adrenalectomy, but more data are required.

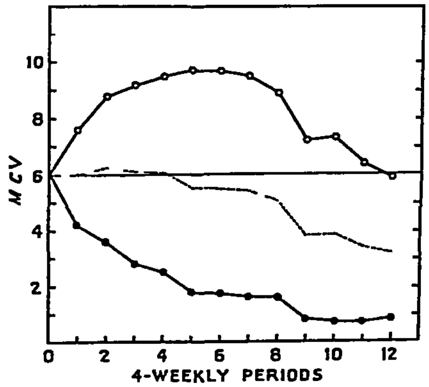

Fig. 4—Calculated effect of selection of patients for hypophysectomy on clinical course of the disease.

The dotted line shows the average M.C.V. for all hypophysectomised patients. The upper line (—○—) shows the M.C.V. of patients with positive discriminants. The lower line (—●—) shows the average M.C.V. of patients with negative discriminants.

The dehydro*epi*androsterone and pooled 11-oxy 17-oxosteroid levels do not seem to have predictive value.

The effect of the menopause and of previous hormone therapy on the excretion of endogenous hormones was described by Hayward et al. (1959), and apparently no improvement in prognosis can be obtained by taking these factors into account. The oestrogens, pregnanediol, and gonadotrophins are most affected by these factors and this may explain why assays of these hormones have been of no prognostic value in this series.

Discussion

The above results show that the response of metastatic breast cancer to adrenalectomy or hypophysectomy can be predicted to a great extent from certain measurements of the hormone environment in which the tumour is growing. The urinary levels of 17-OHCS and ætiocholanolone are two indices of this environment which are of value.

As a practical means of selecting patients for hypophysectomy, the discriminant derived from the 17-OHCS and ætiocholanolone levels appears potentially useful. If the patients in the present series had actually been selected on the basis of their discriminants, 13 of the 25 submitted to hypophysectomy would not have been treated in this way. Of the 13 rejected, 1 would have been denied remission of the disease, 1 could have had a marginal response, and the other 11 would have failed to respond. Although percentages may be misleading with such small numbers of patients, these figures indicate that 85% of those rejected would have failed to respond to hypophysectomy.

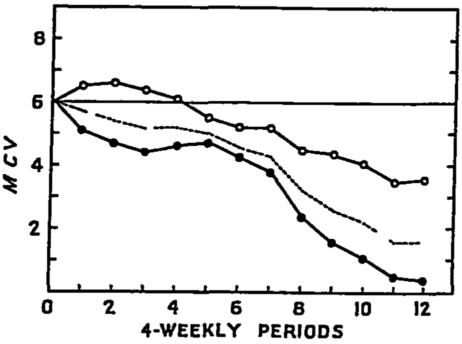

Fig. 5—Calculated effect of selection of patients for adrenalectomy on clinical course of the disease.

The dotted line shows the average M.C.V. for all adrenalectomised patients. The upper line (—○—) shows the M.C.V. of patients with positive discriminants. The lower line (—●—) shows the average M.C.V. of patients with negative discriminants.

Of the 12 patients who would have been selected for hypophysectomy, 7 (60%) would have obtained remission, while the other 5 would have had a marginal response. It must be remembered that in this series we have defined remission so strictly that the overall rate for patients subjected to hypophysectomy is only 32%. A remission rate of 60% would be a very substantial improvement.

If the mean M.C.V. curve for hypophysectomy patients having a positive discriminant is compared with that of hypophysectomy patients with a negative discriminant, the difference in the clinical course is very striking (fig. 4). These results are, of course, retrospective, and a clinical trial would be needed to substantiate them.

The discriminant does not seem to be so useful a means of selection in adrenalectomy. Admittedly, all patients who in fact had an objective remission would have been treated, but a high proportion of those selected for treatment would have failed to benefit Of 13 patients selected, 6 would have obtained remission, 1 would have been in the intermediate group, and 6 would have failed to benefit Although selection is not as effective as in the hypophysectomy series, an overall regression-rate of 46% would have been obtained

Fig 5 shows that when the average M C V curve for all adrenalectomy patients with a positive discriminant is compared with the M C V curve for adrenalectomy patients with a negative discriminant, prognosis would not improve the clinical results to the same extent as in hypophysectomy

Atkins et al (1960) have found that in randomly selected patients hypophysectomy is a better treatment than adrenalectomy From this it follows that some of the patients in our intermediate or failure groups would have obtained remission if they had been treated by hypophysectomy rather than adrenalectomy It is possible that these cases might have been those in the adrenalectomy series who failed to benefit in spite of a positive discriminant In other words, as there is a clinical difference in response, the presence of some cases of failed adrenalectomy having a positive discriminant would be expected

The physiological significance of the results of our hormone assays is obscure Judging by the effects of hormones on the growth of the normal breast in laboratory animals, one might expect that prognosis would be related to the levels of œstrogens, progestins, prolactin, and growth hormone The finding that the 11-deoxy-17-oxosteroids (ætiocholanolone in particular), probably largely derived from adrenal dehydroepiandrosterone, and the 17-OHCS, largely derived from cortisol, have predictive value, is unexpected Very probably these two groups of hormones are merely indices of a particular hormone environment of considerable complexity, and determinations of other blood or urinary hormones might provide much more information about this environment

Our results agree very closely with those of Allen, Hayward, and Merivale (1957), when the differences in the methods are taken into account These authors described a correlation between prognosis and the ratio of the 11-deoxy-17-oxosteroids to the 11-oxy compounds However, Plantin et al (1958) and Hobkirk and Forrest (1957) did not find assays of fractionated 17-oxosteroids useful for prognosis in their cases

Several other reports indicate that differences in urinary hormone levels may be associated with differences in response to therapy Huggins and Dao (1954) found that a high œstrogen level after oophorectomy was associated with successful response to adrenalectomy Loraine et al (1957) showed that, in general, postmenopausal women with a high gonadotrophin level are less likely to benefit from stilbœstrol than those with lower levels of excretion These findings emphasise the fact that the hormonal status of the host is of great importance in determining response to endocrine treatment

Summary

The response of metastatic breast cancer to adrenalectomy or hypophysectomy largely depends on the hormonal environment in which the tumour is growing Of the hormonal factors measured in this series of 59 patients the levels of ætiocholanolone and the 17-hydroxycorticosteroids are of most use in predicting the outcome of the two operations They were particularly valuable in indicating the probable response to hypophysectomy

We should like to thank Mr Hedley Atkins and Dr Kenneth MacLean of Guy's Hospital and Mr Murray Falconer and Mr Peter Shurr of the Guy's-Maudsley Neurosurgical Unit, for permission to investigate their patients We are very grateful to Dr P Armitage for his assistance with some of the statistical problems of this work and to Dr C C Spicer for calculating the discriminant function We should also like to thank Miss Y A Leon, Mr B S Thomas, and Mr W G Hunter for their assistance with the hormone assays

Appendix

Statistical Note by DR C C SPICER

The constants of the discriminant function were calculated using the combined sums of squares and products "within groups" for the successful, intermediate, and failure patients The significance was then tested by the F test for the generalised distance given by Roy and Bose (1940) The value of F is 5 1 on 2 and 33 degrees of freedom and is significant at about the 0 01 level The constants of the function were rounded to convenient numbers as no great accuracy was justifiable

As regards the general validity of the discriminant, its continued success when used on observations other than those from which it was calculated is probably a better justification than a formal test of significance

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DIAGNOSIS OF POLYMYOSITIS

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DERMATOMYOSITIS was defined by Steiner in 1905 as an acute, subacute, or chronic disease of unknown origin characterised by dermatitis and multiple foci of muscle inflammation and œdema Polymyositis has long been recognised as the same disease process in which the skin changes are slight or absent The disease, which has received comparatively little attention in this country (see Bauwens 1956, Nattrass 1956, Richardson 1956, Walton 1956, Walton and Adams 1958), is still little known here and is certainly commoner than has been previously thought We have discovered 28 cases of the disease in ten years at one London teaching hospital

The mode of presentation varies according to the patients' ages, and at all ages polymyositis may mimic other general medical and neurological disorders In some cases the diagnosis cannot be made with certainty, for muscle biopsy may be normal, the electrical findings misleading and the clinical picture atypical Fortunately two of these three diagnostic features are usually positive.

Material and Methods

We describe here our experience of the 28 cases (see accompanying table)

DATA ON 28 CASES OF POLYMYOSITIS

Case no	Sex	Age (yr)	Duration		Main lesion of muscles	Electromyographic findings	Associated features
			Before admission	Since admission			
1	F	49	9 yr	7 yr	Focal necrosis	Polymyositis	Family history positive (?)
2	F	61	6 yr	7 yr	Focal necrosis, sarcoid-like	Polymyositis	
3	F	63	9 mos	2$^1/_2$ yr	Focal necrosis, sarcoid-like	Polymyositis	Pulmonary tuberculosis, iritis
4	M	15	8 yr	1 yr (died)	Diffuse fibrosis	High-voltage polyphasic	Heart-block
5	M	61	1 mo	6 mos (died)	Focal necrosis	Polymyositis	Dermatomyositis (lupus erythematosus, bronchial carcinoma)
6	F	68	8 yr	3 yr (died)	Focal necrosis, sarcoid-like	Polymyositis	
7	F	45	3 yr	5 yr	Normal biopsy	Normal	Adenomata of cervix
8	F	23	12 yr	2 yr	Normal biopsy	Polymyositis	
9	F	68	18 mos	1 yr (died)	Focal necrosis	Dystrophic	Adenocarcinoma of uterus
10	M	6	4 yr	7 yr	Focal necrosis	Dystrophic	Family history positive (?)
11	F	5	18 mos	4 mos (died)	Diffuse fibrosis, inflammation, and neural atrophy		
12	F	77	3 yr	1 yr (died)	Diffuse inflammation		Melæna, myocardial lesions
13	M	50	3 mos	2 yr	Diffuse inflammation	Polymyositis	Raynaud phenomenon, arthritis, albuminuria
14	M	46	7 mos	3 yr	Diffuse inflammation	Polymyositis	Response to neostigmine
15	F	30	4 mos	2 mos (died)	Focal necrosis		
16	F	56	4 mos	3 mos (died)	Diffuse inflammation		
17	F	59	5 yr	6 mos (died)	Diffuse inflammation and fibrosis		
18	F	64	3 yr	8 yr (died)	Diffuse inflammation, dermatomyositis		Adenocarcinoma of uterus, skin lesions
19	F	43	6 yr	17 yr	Focal necrosis	High-voltage polyphasic	Nodular goitre
20	F	67	20 yr	3 yr (died)	Diffuse inflammation with fibrosis		Mild thyrotoxicosis, carc breast
21	M	46	14 mos	7 yr	Focal necrosis	High-voltage polyphasic	
22	F	43	18 mos	1 yr	Diffuse inflammation	Polymyositis	Rheumatoid arthritis
23	M	46	10 yr	2 yr	Focal necrosis	Myopathic, dystrophic	Dermatomyositis
24	F	72	1 mo	3 mos (died)	Diffuse inflammation	-	Carcinoma of clitoris, diabetes mellitus, dermatomyositis
25	F	46	10 mos	4 mos	Diffuse inflammation	Dystrophic	
26	M	34	4 mos	11 yr	Diffuse inflammation	Dystrophic	
27	F	52	9 mos	1 yr	Diffuse inflammation	Normal	
28	F	15	3 mos	1 yr	Mild focal necrosis	Normal (see text)	

We use the word "myopathy" for disease of muscle, "myositis" for inflammation of muscle, and "muscular dystrophy" for a purely degenerative process

Strength-duration curves were done by Miss T Wareham using the 'Multitone' constant-voltage stimulator Electromyograms were done with concentric needle electrodes, in collaboration with Dr Euan Campbell

Modes of Presentation

"*Myopathy*"

In patients of all ages polymyositis is easily confused with non-familial chronic muscular dystrophy Nattrass (1954) pointed out that several cases closely resembling pseudohypertrophic muscular dystrophy and diagnosed as such by neurologists had eventually recovered fully He suggested that 5 out of 7 of these patients had had polymyositis

Case 10—This patient had been admitted to hospital at the age of 6 in 1952 He had walked normally at 18 months, but at the age of 2 years pain in the legs and difficulty in walking had developed By 3$^1/_2$ years he could hardly sit up, and the calf muscles were noted to be bulky From the age of 5 years he improved a little His intelligence was normal, and the cranial nerves were unaffected The arms showed pseudohypertrophy of the deltoid and biceps, and these muscles felt wooden, power was normal but the arm-jerks reduced There was symmetrical pseudohypertrophy of the calf muscles He walked with a wide, unsteady gait and the extensors of the feet and toes were weak The knee and ankle jerks were reduced, plantar responses were flexor, sensation was normal He was discharged after a muscle biopsy and was treated with vitamin E A year later he had improved and could ride a tricycle and walk upstairs easily By November, 1954, he was progressing well and could swim In the spring of 1956 he relapsed after an attack of abdominal pain, the pain in the legs recurred, and he could no longer stand or walk

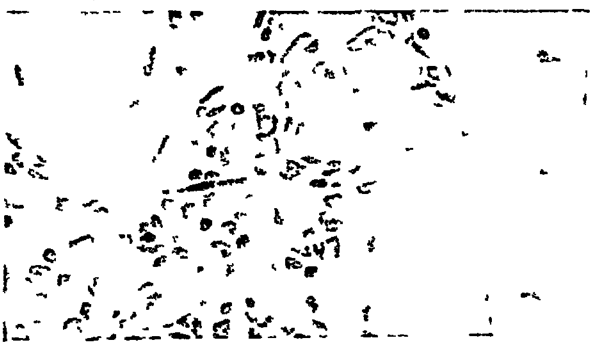

Fig 1—Case 10 endomysial cell proliferation and inflammatory infiltration replacing necrotic muscle-fibre adjacent muscle-fibre regenerating (Hæmatoxylin and eosin ×300)

Reviewing the muscle sections in 1958, we were impressed by evidence of fibre regeneration and inflammatory-cell infiltration (fig 1), neither of which is found in true muscular dystrophy The patient was readmitted, and his condition then closely resembled advanced pseudohypertrophic muscular dystrophy Treatment with prednisolone produced slow but definite improvement in the power of his limbs

In this case and in case 1 the diagnosis of muscular dystrophy was apparently confirmed by a positive family history, but in neither could proof of this diagnosis be obtained by examination of the affected relative 8 of our cases of polymyositis showed pseudohypertrophy

In other cases, notably in older patients, polymyositis presents as a condition resembling muscular dystrophy without pseudohypertrophy The two conditions may be indistinguishable clinically, but in polymyositis there is greater variation in the distribution of the muscular weakness, and wasting of the tongue and neck muscles, with dysphagia, dysarthria, and laryngeal stridor, pronounced involvement of distal muscles, and the early development of contractures also point to this diagnosis

Case 4—At the age of 16 the patient was referred as a case of facioscapulohumoral dystrophy At the age of 7 contractures of biceps with inability to extend the arms, and a year or so later contractures of the tendo achillis, had developed The condition remained stationary till the age of 14 when he developed laryngeal stridor followed by weakness of the voice and dysphagia for solids and nasal regurgitation of liquids The principal findings clinically were bilateral facial weakness, paralysis of the palate, weakness of the voice, laryngeal stridor, wasting and fibrillation of the tongue, stiffness and weakness of the neck muscles, symmetrical proximal muscular weakness and wasting of all four limb muscles with contracture of the

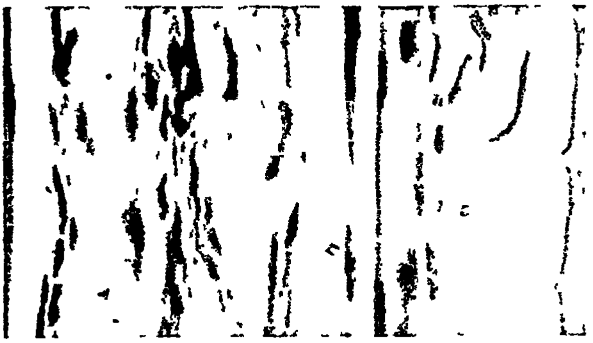

Fig 2—Case 4 diffuse fibrosis of muscle with atrophy of intervening muscle-fibres (Hæmatoxylin and eosin ×300)

biceps, bilateral pes cavus, areflexia, partial heart-block Pathologically diffuse fibrosis of muscle was present in some areas with mild focal necrosis and regeneration in others (fig 2)

Nattrass (1956) pointed out that in myositis tendon reflexes may be brisk at a stage where in true muscular dystrophy they would be reduced or absent Other pointers to a diagnosis of myositis are rapid onset of weakness or spontaneous remission of the disease

Menopausal Myopathy

The late myopathies of Nevin (1936) and Shy and McEachern (1951) are characterised by necrosis of muscle-fibres and inflammation—which are not features of familial muscular dystrophy None of their cases was familial Adams et al (1953)—unlike Nevin—were convinced that these late cases of myopathy were really a form of myositis

Inasmuch as the pathological changes of polymyositis and dermatomyositis are indistinguishable from those of menopausal myopathy, it seems to us that Adams et al are correct, although in these cases—as in many forms of chronic polymyositis—fever, leucocytosis, or other evidence of inflammation is rare We had 10 such cases in our series, and in 3 the pathological evidence of inflammation was so pronounced that a diagnosis of sarcoidosis was suggested

In this group women predominated Clinically the group was not otherwise homogeneous, for, although in 2 the condition was localised to the quadriceps, all the others had more widespread muscular involvement which in 1 progressed to fatal bronchopneumonia associated with severe generalised weakness

Myasthenia Gravis

Both in polymyositis and in myasthenia gravis there may be pathological fatigability and partial response to neostigmine with involvement of the facial muscles and of speech and swallowing (Matthews and Burne 1953) 1 of our cases responded to neostigmine, but this patient had slight fever, increased erythrocyte-sedimentation rate (E S R), albuminuria, and slight skin lesions which distinguished his disease from myasthenia gravis, and spontaneous fluctuations in muscle weakness were not as evident as in true myasthenia

Motor-neurone Disease

Confusion between an inflammatory disease of muscle, however chronic, and motor-neurone disease may seem unlikely But in 2 of our patients motor-neurone disease was considered The difficulty in distinguishing the two diseases arises because in polymyositis the tendon reflexes may be brisk and spontaneous fasciculation may occur, we observed fasciculation with wasting of the tongue in 3 of our patients (cases 4, 5, and 20) The affected muscles are often denervated, and electromyography may show high-voltage potentials suggesting anterior-horn-cell disease Where these changes coexist the distinction from motor-neurone disease may be difficult and only muscle biopsy may distinguish the one from the other

Peripheral Neuropathy

An increase in the protein content of the cerebrospinal fluid points strongly to a diagnosis of motor peripheral neuropathy—which otherwise may not be easily distinguishable from polymyositis

In some cases of polymyositis it may be impossible to tell clinically whether the lesion is in the spinal cord, motor nerves, or muscle

Case 28 —A girl, aged 15, had had weakness of the fingers for three months Examination revealed symmetrical weakness and wasting of the forearms and small muscles of the hands with flexion contracture of the fingers The tendon reflexes were brisk in the arms and elsewhere, and there was no other weakness The other systems were normal, and there was no rash Creatinuria was the only abnormal biochemical finding Biopsy of the forearm muscles was normal apart from one small area of muscle necrosis We found the electromyogram to be normal but referred the patient to Dr A T Richardson, who found one area in the muscle somewhat suggestive of polymyositis Diagnoses considered were syringomyelia without sensory loss, peroneal muscular atrophy, distal myopathy, dystrophia myotonica, and peripheral neuritis, but the likeliest appeared to be polymyositis With administration of prednisolone, improvement began after three or four months, and eight months later muscle power in the hands was normal, the dose was gradually reduced, and the drug was finally discontinued without relapse.

Our series included 2 somewhat similar cases (cases 7 and 8) in which either the clinical features or the investigations (including the electrical reactions) supported the diagnosis but the histological changes did not, or vice versa

Differential Diagnosis from General Medical Conditions

Collagen Diseases

Polymyositis can be regarded as " dermatomyositis without the rash ", but a dermatologist may sometimes detect an inconspicuous rash This is usually telangiectatic and situated on the extensor aspect of the forearm the hand, and the face, patches of scleroderma may be found on the face or forearm, and sclerodactyly may be present Calcinosis may also be present, although we had no examples

Of the other collagen diseases, rheumatoid arthritis, systematic lupus erythematosus, and generalised scleroderma may be accompanied by polymyositis In rheumatoid arthritis pathological changes in the muscles are similar to those of polymyositis but are usually slighter In this condition muscular atrophy around the affected joints is a long-recognised feature, and there may be fasciculation and brisk tendon reflexes Muscular weakness apart from that associated with pain is unusual

In systematic lupus erythematosus there is likely to be evidence of involvement of other tissues, but occasionally there is evidence of symmetrical peripheral neuropathy In none of our cases of polymyositis were L E cells found in the peripheral blood

In scleroderma skin changes predominate, but muscular wasting and weakness are common and the muscles show mild inflammatory changes

Polyarteritis nodosa can be distinguished from polymyositis by the peripheral neuropathy which usually underlies the muscular weakness, and by sensory changes which are almost invariably present In polyarteritis nodosa symptomless muscle involvement secondary to vascular changes is common, so random muscle biopsy is useful Caldwell (1955) believes that some fulminating cases of dermatomyositis are due to very severe polyarteritis, and Mac Keith (1944) described cases in which asymmetrical muscle weakness arose from infarction and was associated with subcutaneous œdema

Thyrotoxic Myopathy

In some cases of thyrotoxicosis progressive muscular weakness and wasting amounting to proximal myopathy are the presenting features These cases of thyrotoxic myopathy are characterised by loss of weight, and fasciculation may occur, but other signs of thyrotoxicosis are usually inconspicuous The condition is equally common in each sex in the older age-groups (McEachern and Ross 1942) The pathological changes in the muscles in the series of Hed et al (1958) were slight except in 2 of their 18 cases which showed extensive fibre necrosis

2 of our patients were originally thought to have thyrotoxic myopathy because of the presence of a goitre In one (case 19) there was no clinical or biochemical evidence of thyrotoxicosis, and removal of a colloid goitre did not affect the muscular disease, which was pathologically a myositis localised to the quadriceps In the other patient (case 20) the radioactive iodine uptake and basal metabolic rate were both at the upper limit of normal, and glucose tolerance was impaired Improvement followed thyroidectomy but was not sustained, and the patient died three years later from increasing muscular weakness The muscular changes were severe, and reviewing her case we believe that she had polymyositis The absence of complete recovery after partial thyroidectomy was more in keeping with this diagnosis as most cases of thyrotoxic myopathy recover fully after resection of the gland A raised basal metabolic rate was found in 8 of our patients with polymyositis, but other tests of thyroid function distinguished these from cases of thyrotoxic myopathy

Sarcoidosis

That muscular lesions occur in sarcoidosis has long been known, but their frequency was formerly underestimated as the muscles were not usually examined histologically Bates and Walsh (1948) suggested that pathological changes were so common that muscle biopsy is the most certain method of diagnosis Whilst these microscopic changes usually give rise to no symptoms, a few cases have been reported in which they were associated with muscular weakness resembling muscular dystrophy (Krabbe 1949, McConkey 1958), in these there was evidence of sarcoidosis of other tissues Sarcoidosis, like polyarteritis nodosa, is diagnosed on a suggestive constellation of symptoms and signs together with histological appearances in a biopsy specimen—usually of skin, lymph-node, or liver

In 3 of our patients (cases 2, 3, and 6) the muscle lesion resembled sarcoidosis with focal epithelioid-cell collections and giant cells (fig 3) In case 3 there was a history of pulmonary involvement earlier in life, followed by attacks of iridocyclitis, but the pulmonary lesions may have been tuberculous in view of subsequent apical calcification In none of the 3 cases was there any clinical or pathological evidence of sarcoidosis, such as increased E S R or hypergammaglobulinæmia, nor was there any evidence of sarcoidosis outside the muscles Skin biopsy on two occasions failed to reveal sarcoid lesions, and in 2 of them (cases 3 and 6) biopsy after inoculation with sarcoid material was also negative

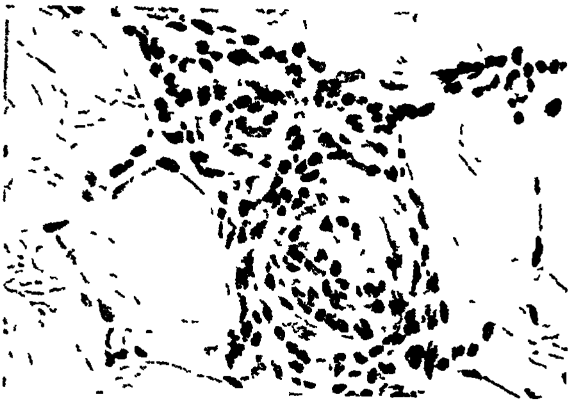

Fig 3—Case 2 focal necrosis of muscle-fibres with macrophage infiltration and epithelioid and giant-cell formation (Hæmatoxylin and eosin ×370)

Histological findings in muscle alone will not distinguish the necrotic type of polymyositis from widespread sarcoidosis the diagnosis of sarcoid can be proved only by showing that a similar reaction is present in other tissues From the absence of other sarcoid lesions clinically in our cases and from the negative results of investigation, we feel that these cases were in fact of polymyositis, but sarcoidosis should be remembered as a cause of myopathy, and cases must be fully investigated to exclude this diagnosis

Carcinoma

The association of dermatomyositis and polymyositis with carcinoma is illustrated in 5 of our 28 cases

In case 18 carcinoma of the body of the uterus developed three years after the muscular disorder had become inactive, the patient died from pelvic metastases five years later without reactivation of the polymyositis Case 5 had had lupus erythematosus six years before he was admitted to hospital with fulminating dermatomyositis, X-ray of the chest revealed carcinoma of the bronchus (Garrod 1959) Case 20 was referred to hospital with carcinoma of the breast, having had chronic muscular weakness for more than twenty years In cases 9 and 24 severe polymyositis resulted in death in under three months, both patients had had a carcinoma successfully removed a year before 1 (case 24) was a diabetic who had carcinoma of the clitoris and dermatomyositis, the other case (9) had had carcinoma of the body of the uterus without skin lesions A 6th patient (case 7) had weakness and wasting of the quadriceps muscles and areflexia, but muscle biopsy was normal, now, five years later, adenomatosis of the cervix has developed

There do not appear to be any clinical or pathological differences between the cases in which carcinoma develops and the others in which it does not, and they must all be scrutinised repeatedly for evidence of neoplasia The incidence has varied in different series from 6 7% (Christiansen et al 1956) to 11% (Scheuermann 1951) The nature of the association is obscure, but, as in carcinomatous neuropathy, there is likely to be some biochemical abnormality

Methods of Investigation

Muscle Biopsy

This is the most satisfactory method of establishing the diagnosis, though in polymyositis the microscopic appearances may be normal or non-specific

Histological changes are often patchy through the muscle, and care must be taken in selecting the muscle for biopsy The methylene-blue technique of Coërs and

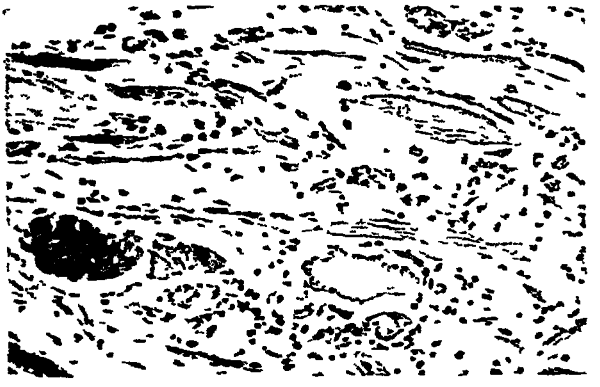

Fig 4—Case 16 diffuse inflammation and œdema with widespread necrosis of muscle-fibres (Hæmatoxylin and eosin ×120)

Wolff (1959) requires special training and is not generally available Weddell (1957) recommends a punch technique in which the muscle is sampled in several different areas

Of our series of 28 cases, 26 cases had an abnormal muscle biopsy The changes fell into two broad groups—focal necrosis and diffuse inflammation and both types of change were sometimes found together When necrosis predominated this was often focal and confined to a single fibre or part of a fibre Inflammatory reaction related to the necrosis also varied from slight proliferation of endomysial cells to pronounced epithelioid proliferation with giant cell formation (see fig 3), occasionally the infiltration was polymorphic

In cases of diffuse infiltration of muscle there was a little secondary muscle necrosis with regeneration but widespread lymphocyte, plasma-cell, and macrophage infiltration between the fibres was the predominating feature (fig 4) Fibroblastic proliferation was usual and proceeded to diffuse fibrosis in chronic cases In 2 (cases 11 and 21) there was in addition neural atrophy of muscles apparently due to involvement of intramuscular branches in the fibrotic process, confirming the electrical evidence of partial denervation in many Although the inflammatory change and the focal lesions were usually dissimilar, extensive necrosis with widespread inflammation is indistinguishable from primary inflammation Whatever the pathological lesion the modes of clinical presentation are the same

Electrodiagnosis

The typical electrodiagnostic findings in polymyositis are a myopathic electromyographic pattern together with evidence of partial denervation this latter may be obtained either from the electromyogram (fibrillation potentials) or from abnormal strength-duration curves The presence of partial denervation distinguishes polymyositis sharply from the chronic muscular dystrophies, even though the electromyogram alone may be indistinguishable The following points may be noted

1 On needling the muscle it may be evident that much fibrosis is present

2 Many polyphasic potentials of short duration and *normal* amplitude suggest polymyositis rather than a chronic muscular dystrophy

3 The changes may be localised within the substance of individual muscles, normal patterns alternating with typical dystrophic and " polymyositic " patterns

In this series electromyograms were done in 20 cases Typical appearances were seen in 9, and those of chronic muscular dystrophy in 5, the appearances were normal in 3 and misleading in 3 In these 3, high-voltage (up to 3 mV) long-duration action potentials were present with a reduced interference pattern—a condition usually attributed to anterior-horn-cell disease although these cases were proved to have polymyositis pathologically In these cases re-examination, with testing of a much wider range of muscles, disclosed the typical findings

Evidence of denervation was found in all but 2 of our cases This suggests that the condition is nearly always to some extent a neuromyositis, although the degree of denervation is usually slight

Electrodiagnosis must always be supplemented by biopsy in the diagnosis of polymyositis

Other Pathological Investigations

Other pathological investigations do not help in diagnosis In the more acute cases the E S R is increased, and there may be slight polymorph leucocytosis The urinary creatine was increased in all our cases, varying from 50 to 500 mg daily With cortisone treatment the rate of excretion lessened but in only 1 case did it fall to the normal range Creatinuria, which occurs in any disease with muscular wasting, is of no value in diagnosis The serum-aldolase does not distinguish the primary muscular diseases from one another but can be useful in distinguishing them from neurogenic disorders

In doubtful cases a therapeutic trial of steroids may be justified Prednisolone 20–30 mg daily in chronic cases, and more in acute cases, may be given to induce a remission Unfortunately not all cases respond to this treatment, which has its own special dangers

Summary

Dermatomyositis, polymyositis, carcinomatous myopathy, and the collagen diseases with muscle involvement fall into the same clinical group

In polymyositis the presence or absence of skin lesions depends on unknown variables Minor lesions may be of diagnostic value

Pathological changes are of two main types—primary muscle necrosis and primary interstitial inflammation Intermediate forms occur, and normal biopsy appearances do not exclude the diagnosis The disease is patchy in the affected muscles, and this distribution can be demonstrated electrically

Electrodiagnostic evidence of partial denervation is very common

We are very grateful to the physicians and pathologists at the hospitals where we work for permission to publish their cases

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CONGENITAL HYPOTHYROIDISM WITH GOITRE

ABSENCE OF AN IODIDE-CONCENTRATING MECHANISM

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THE initial step in the synthesis of the thyroid hormones is the selective accumulation of iodide in the gland This has been termed the "iodide trap" or the "iodide pump" Its intimate nature is unknown (Wyngaarden et al 1951, Halmi and Stuelke 1959), but it appears to require an expenditure of energy, for it fails in thyroid tissue slices under anaerobic conditions or if these are exposed to substances which impair respiration (Slingerland 1955) An iodide pump has also been demonstrated in the salivary glands (Honour et al 1952, Freinkel and Ingbar 1953, Rowlands et al 1953, Fellinger et al 1956) and in the gastric mucosa (Davenport 1943, Myant et al 1950, Halmi and Stuelke 1955)

This paper reports studies on a patient with lifelong hypothyroidism who developed a goitre at the age of 15 Not only did his thyroid fail to concentrate iodide but his salivary glands and his gastric mucosa also lacked an iodide pump A strong family history for thyroid disease and the remarkable consanguinity of his forebears suggests that the defect is genetically determined

Case-report

He was born at full term after a normal pregnancy Birthweight was 6 lb 10 oz At 6 months a barium enema, performed because of obstinate constipation, was normal An umbilical hernia was treated by taping until he was 3, when it was repaired surgically He first sat at 6 months, had his first tooth at 13 months, and walked at 14 months

He did poorly during his first 3 years of school and was said to have been shorter than his classmates At age 8 the basal metabolic rate was minus 29% (Aub and DuBois), and serum-cholesterol concentration was 560 mg per 100 ml X-rays of his bones showed a delay of approximately 3 years in maturation The sella turcica was slightly deepened and enlarged When given one grain daily of desiccated thyroid he became more active and his school performance improved dramatically 2 years later X-rays were reported to have shown normal bony maturation Puberty was normal

3 months before admission at 15 years of age a slight swelling of the neck was observed by the mother, who then discontinued his thyroid medication Within a month, when he had become fatigued, lethargic, costive, and had gained 20 lb, he was referred to one of us (E M C)

Family History

There were three consanguine marriages among his immediate forebears (fig 1) Both parents came to the United States from a small district of Austria which is now annexed to Poland In their family groups intermarriage has been commonplace Many instances of goitre are known, and several have been removed The patient's father has a thyroid which is two to three times normal size The patient's mother and maternal grandmother have had numerous local mastectomies for cystic disease

Condition on Admission

Blood-pressure, respirations, and heart-rate were normal He weighed 10 st 12 lb, and his height was 5 ft $3^3/_4$ in He seemed of normal intelligence The skin was dry and moderately pigmented Axillary and pubic hair and genitalia were normal The thyroid was about three times normal size and contained numerous small nodules There was no sialorrhœa, and saliva was seen to flow from both parotid and submaxillary ducts The remainder of the physical examination was normal The basal metabolic rate was minus 39% Total serum-iodine concentration was 1 5 µg per 100 ml, and protein-bound iodine 0 5 µg per 100 ml Serum-cholesterol concentration was 320 mg per 100 ml Routine blood and urine tests were normal The sella turcica was at the upper limits of normal or slightly larger than normal size, but there was no erosion of the clinoids X-rays of the chest and bones otherwise were normal Bone age was consistent with chronological age

Biopsy of Thyroid

After a period of study the patient underwent a surgical exploration and biopsy of his thyroid The gland contained numerous small nodules Some were cystic but most were cellular Microscopic examination disclosed numerous cellular adenomas and intense hyperplasia of the parenchymal elements (fig 2) There was scarcely any colloid to be seen Although some nuclei were pyknotic and atypical, the findings were not those of malignant change

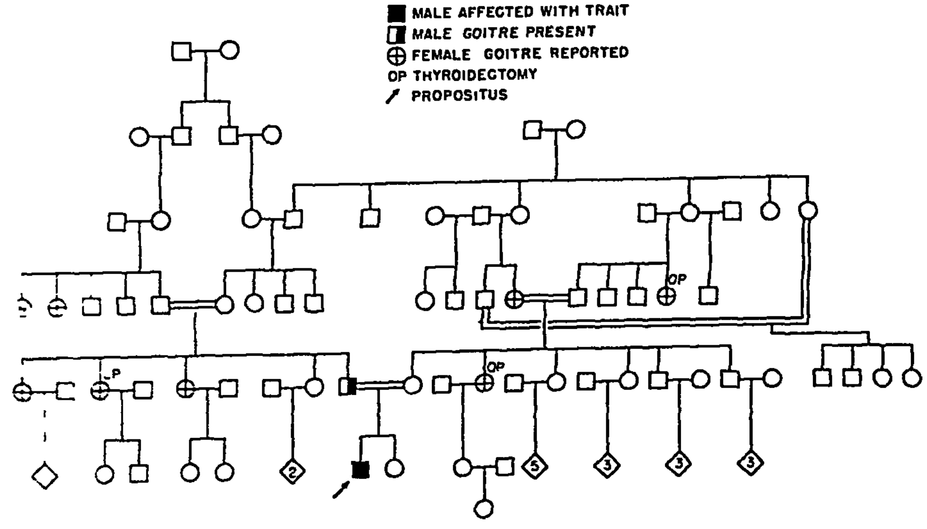

Fig 1—The genetic chart The double lines represent consanguine marriages The inserted numbers refer to siblings of unknown sex

Tracer Studies

Methods

Measurements of labelled iodine in vivo were made initially after oral administration of ^{131}I in a three-way scintillation counter A second tracer of ^{131}I was given intravenously, and measurements were taken with a collimated Geiger-Mueller counter at 40 cm The labelled iodine of serum, saliva, urine, and gastric fluid was measured in a well-type scintillation detector

Sputum was collected under supervision with or without a small bit of wax in new glass containers The corresponding blood sample was taken as nearly simultaneously as possible Thiocyanate in serum and sputum was determined by the

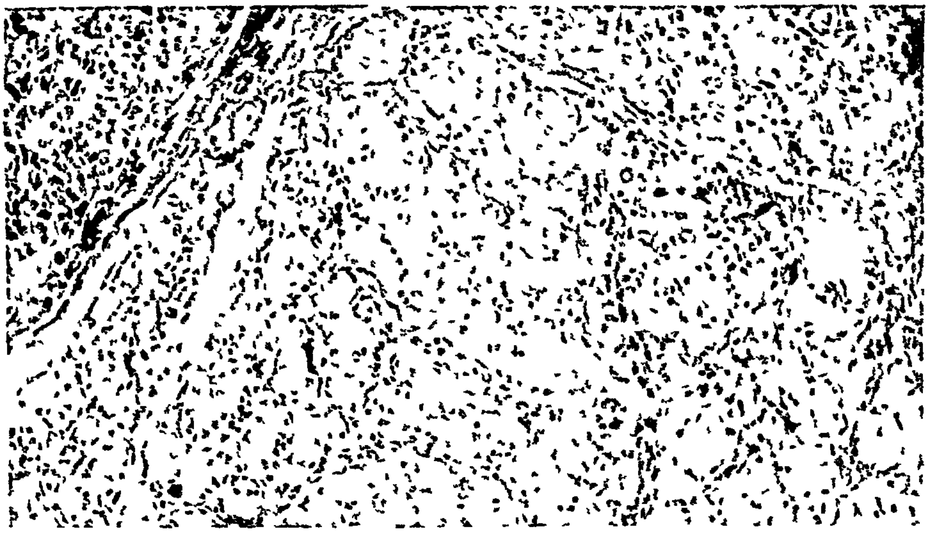

Fig 2—The histological appearance of the thyroid gland Note the adenoma and the intense hyperplasia of all the tissue elements

method of Griffith and Lindauer (1937), chloride by the method of Schales and Schales (1941), creatinine by the method of Peters (1942), and amylase by the method of Huggins and Russell (1948) Stable iodine was determined by a modification of the method of Barker (1948)

The thyroid biopsy specimens were brought at once on ice to the laboratory and were cut as quickly as possible with the Stadie microtome Approximately 150 mg of tissue were added to flasks containing 4 ml of 0·1 *M* phosphate buffer at pH 7·4 Some flasks contained 10^{-3} *M* thiouracil, and some approximately 0·1 µC of ^{131}I without added carrier After incubation at 37°C for an hour the slices were removed, gently blotted, weighed, and homogenised in 2 ml of buffer Aliquots were taken for determination of labelled iodine, for direct chromatography, and for proteolytic digestion before extraction with butanol and chromatography Aliquots of the suspending medium were also taken for measurement of labelled iodine and for chromatography

Chromatography of serum, urine, saliva, and thyroid tissue homogenate and digest was in butanol/acetic-acid water and butanol/ethanol/ammonia solvent systems Digestion of tissue samples was at pH 8·2 for 48 hours in the presence of crude pancreatin Butanol extraction of the samples proved to be quite complete.

Results

Only a small fraction of the administered ^{131}I accumulated in the thyroid 24 hours after an oral dose 11·4% was in the gland, and at 48 hours 7·8% The labelled iodine in the tissues subtended by the collimated counter at 2 minutes corrected for residual radioactivity was 14·0% of the injected dose, and this value slowly fell thereafter A significant proportion of this may be assumed to have been in the vascular space of the hyperplastic thyroid and in the other vascular structures of the neck. 67·5% of the administered ^{131}I appeared in the urine within the first 24 hours, and 86·3% in the first 48 hours The concentration of labelled iodine in the serum at 48 hours was 0·40% per litre and that of protein-bound ^{131}I was 0·041% per litre. Chromatography of samples of serum and urine obtained during the first 24 hours showed that inorganic iodide was the only ^{131}I-labelled substance The samples were more than 95% extractable with acid butanol

The concentration of iodide in the saliva was not significantly different from that in the serum These results appear in the table, together with those obtained from several relatives of the patient and from a series of subjects with various other conditions Some of the salivary ^{131}I/serum trichloroacetic-acid-soluble ^{131}I ratios (S/P ratio) for the patient were slightly in excess of 1 These were in each case determined on a falling serum concentration curve Any delay in salivary flow or any residual saliva in the mouth at the time of sampling would increase the ratio, and accordingly the ratios should be corrected downward It is seen from the table that both parents, sister, and maternal aunt of the patient had S/P ratios comparable to those of the control subjects The amylase concentration of a specimen of saliva was 28,800 Russell units per ml

The S/P ratio for chloride was considerably less than 1 and was comparable to values found in other subjects On the other hand, the S/P ratios for thiocyanate indicated little, if any, active concentration by the salivary glands The level of thiocyanate in the serum of the patient was 0·4 mg per 100 ml, a normal value

The ratio of ^{131}I in gastric fluid collected 5 hours after administration of the ^{131}I and half an hour after introduction of the gastric tube was 0·8 The pH of the gastric fluid was 2·0

Renal clearance of ^{131}I was measured successively for one 2-hour period and two 1-hour periods and compared to endogenous creatinine clearance. This study was done 24 hours after administration of ^{131}I when the serum concentration of labelled iodide was falling only slowly Serum was obtained at the mid-points of the urine collection periods and the calculations were based on the trichloroacetic acid soluble ^{131}I of the serum Iodide clearances were 23·8, 18·9, and 20·2 ml per minute for the three successive periods Corresponding creatinine clearance values were 48·8, 37·0, and 49·1 ml per minute The iodide clearances are interpreted as normal The low values for endogenous creatinine clearance may be related to the myxedematous state of the patient.

Tissue slices cut at random from the biopsy fragments failed to accumulate ^{131}I from the medium in which they were

THE CONCENTRATION RATIOS BETWEEN SPUTUM AND SERUM OF IODIDE, THIOCYANATE, AND CHLORIDE IN THE PATIENT (A), IN SEVERAL MEMBERS OF HIS FAMILY, AND IN CONTROL SUBJECTS

S, concentration in saliva P, concentration in serum The ^{131}I ratio is based on trichloroacetic-acid-soluble ^{131}I

—	Sex	Age	Diagnosis	Time after ^{131}I (hr)	S/P		
					^{131}I	SCN⁻	Cl⁻
A	M	15	Goitre, hypothyroid	48	0·89	1·0	0·21
				1	1·46		
				2	1·64		
				3	1·31	1·6	0·40
				4	1·78		
				5	1·07		
B[1]	M	50	Nodular goitre	2	64·3	10·2	0·15
C[2]	F	21	Normal	2	29·7	13·0	0·15
D[3]	F	54	Normal	2	53·4	26·0	0·46
E[4]	F	49	Normal	1	21·4	10·0	0·10
				2	43·0	13·0	0·69
F	M	59	Thyrotoxicosis	2	10·9	8·9	0·14
G	F	42	Normal	2	27·7	4·1	0·11
H	F	43	Thyroid carcinoma	2	28·3	16·0	0·18
I	M	67	Normal	2	33·3	6·5	0·15
J	F	45	Previous thyrotoxicosis	2	30·8	17·2	0·10
K	F	60	Previous thyrotoxicosis	2	22·6	13·0	0·22
L	F	11	Hashimoto's thyroiditis	6	47·1		
				24	15·5		
				48	59·0	14·8	0·11
M	M	42	Hypothyroid	2	25·9	15·5	0·16
N	M	51	Myxedema	2	48·1	12·5	
O	F	52	Normal	2	70·2	9·0	0·33
P	F	28	Previous thyrotoxicosis	2	44·1	20·2	0·16
Q	M	30	Goitrous cretin[5]	2	35·7	8·1	0·17
R	F	39	Euthyroid		22·7	13·3	
S	F	41	Simple goitre	2	19·1	11·8	0·14
				4	32·4	16·0	0·12

1 Father of A 2 Sister of A 3 Maternal aunt of A 4 Mother of A 5 Previously reported (Stanbury et al 1955)

incubated This was observed both with and without 10^{-3} *M* thiouracil in the medium The ratios of ^{131}I-iodide per gramme thyroid to ^{131}I-iodide per ml medium were 0 65 and 0 99 in the two flasks with thiouracil, and 0 65 and 0 67 in the two without thiouracil The ^{131}I-iodide in these ratios is the amount present as inorganic ^{131}I as determined by chromatography There was no more protein-bound ^{131}I in slices incubated for an hour with ^{131}I than in control slices A small amount of protein-bound ^{131}I initially present in the slices was formed from the two tracer doses of ^{131}I administered several days before biopsy Digestion with pancreatin, extraction with butanol, and chromatography both in alkaline and acid solvent systems disclosed that approximately three-quarters of the protein-bound iodine was monoiodotyrosine, and a quarter diiodotyrosine Little, if any, iodothyronine was detected Over 90% of the ^{131}I which was present in the supernatant after centrifuging the homogenate at 100,000×g was precipitated between 1 6 and 1 95 *M* phosphate These are the conditions of thyroglobulin precipitation

The iodine content of the gland was unusually low Two samples of biopsy material were weighed, homogenised, and analysed for iodine Concentrations of total and protein-bound iodine in one fragment were 4 43 and 4 23 µg ^{127}I per g wet tissue, and 4 85 and 3 53 in a second Assuming a total gland weight of 60 g, one may estimate a total thyroid iodine of approximately 250 µg The normal thyroid contains several milligrammes of iodine

Discussion

The findings in our patient indicate that there is no iodide pump in his thyroid, salivary glands, or gastric mucosa In spite of a large and intensely hyperplastic goitre, only a small fraction of an administered dose of ^{131}I entered the gland and became protein-bound This finding in itself is consistent with a failure of iodide trapping The small amount of protein-bound iodine in the gland is attributable to iodide which entered the gland by simple diffusion Further, in-vivo measurements of the secretion of gastric and salivary glands disclosed that these structures also were unable to concentrate iodide

The normal thyroid maintains a concentration of inorganic iodide which is twenty to thirty times that of the serum (VanderLaan and VanderLaan 1947) Similarly, the concentration of iodide in the saliva is many times that in the serum (S/P ratio) (Myant et al 1950, Honour et al 1952, Freinkel and Ingbar 1953, Rowlands et al 1953, Fellinger et al 1956) The S/P ratio is higher for serous (parotid) than for mixed saliva (Honour et al 1952), and is lowered when the salivary secretion-rate is raised (Fellinger et al 1956) The ratio is not altered by iodide deficiency or by methyl thiouracil or mercaptoimidazole (Edwards et al 1954), nor is it correlated with thyroid function (Gabrielsen and Kretchmar 1956), but it is reduced to 1 0 or less by large doses of perchlorate Freinkel and Ingbar (1953) were unable to lower the ratio below 2 8 by giving large amounts of thiocyanate

Thiocyanate is also concentrated by the salivary glands, and the gradient is lowered by administration of iodide or perchlorate (Edwards et al 1954) Although iodide is discharged from the thyroid by thiocyanate, there is no accumulation of thiocyanate in the thyroid (Wollman et al 1958) In this respect the thyroid pump seems to differ from that of the salivary glands

The gastric mucosa concentrates iodide to approximately the same degree as the thyroid and salivary glands (Myant et al 1950, Halmi and Stuelke 1959) and quite independently of the acidity of the gastric secretion (Mason and Block 1950) The concentration gradient is also reduced by thiocyanate and perchlorate (Halmi and Stuelke 1959)

Studies on the biopsy specimens from the thyroid of the patient confirmed the in-vivo observations Tissue slices were unable to concentrate iodide or to make an appreciable amount of protein-bound iodine The small amount of protein-bound iodine formed from the ^{131}I given several days before the biopsy was present mostly in the form of monoiodotyrosine and smaller amounts of diiodotyrosine The total amount of iodine in the gland was remarkably small and consistent with a process limiting the entry of iodide into the gland

The possibility is not excluded that a dietary or endogenous metabolite having an effect similar to perchlorate could be responsible for the findings It seems improbable that a dietary factor could have been present all his life The favoured hypothesis is that he lacks an essential component of the iodide pump It is purely speculative at present whether the missing factor is a transport or cell-surface substance or an essential component of the energy-supply system of the pump

So far as we know, this is the first demonstration that a patient may be hypothyroid and have a goitre because of an absence of the iodide pump Federman et al (1958) reported a 19-month-old infant with cretinism and a goitre who failed to accumulate iodine in the gland They surmised that the thyroid of their patient might be unable to take iodide from the blood Others have reported similar patients who may belong to this special category of goitrous cretinism Mosier et al (1958) tested the capacity of two of their goitrous cretins to concentrate iodide in the saliva and found it to be normal in each case The defect in thyroid function of our patient is distinct from the several metabolic anomalies which have been described in other goitrous cretins and recently reviewed (Stanbury and McGirr 1957)

It was disappointing not to find evidence of impaired salivary iodide secretion in the parents or other relatives of the patient The strong family history of thyroid disease and the consanguinity of his parents suggests that one or both parents is heterozygous for the same defect One need not necessarily suppose that a heterozygote would have any detectable limitation in his iodide pump, especially when the pump is working well below capacity

Summary

A patient is described who has been hypothyroid from birth, except when receiving thyroid medication A goitre was first recognised when he was 15 There were three consanguine marriages in his forebears, and thyroid disease was common in the family

Studies disclosed a very low uptake of ^{131}I by the thyroid The salivary glands and the gastric mucosa were unable to concentrate iodide

Histological examination of a biopsy specimen revealed intense hyperplasia Tissue slices from the biopsy did not accumulate significant amounts of ^{131}I in vitro

The findings are interpreted as indicating that the hypothyroidism and goitre resulted from a genetic defect in the iodide-concentrating mechanism

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Addendum

On the assumption that the consequences of a defective thyroidal pump could be overcome by a high concentration of iodide in the blood, the patient was given 1 mg of potassium iodide, three times daily, at the time of discharge from the hospital In 4 weeks his basal metabolic rate steadily rose from minus 38 to minus 1 The signs and symptoms of hypothyroidism disappeared, and the goitre diminished to about one-third of its size after the biopsy

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BACK PAIN AND HYPERÆSTHESIA

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BACK pain, widespread in our modern civilisation, is poorly understood Diagnosis is largely a question of appending a regional name, such as lumbago, treatment is diverse, and follow-up is often avoided because uncertainty and confusion surround the subject But this common cause of unnecessary pain and loss of man-hours can be localised accurately and treated with confidence

In industrial practice the syndrome of pressure on a nerve-root by a protruded intervertebral disc is rare But there is a different syndrome, which may arise at any spinal level from the occiput to the coccyx, and comprises

1 A clearly defined area of hyperæsthesia adjacent to the spine
2 A localised tender spot (paravertebral) associated with the area of hyperæsthesia
3 A dull ache in the same area
4 Limitation of movement of the trunk by pain

Whilst the exact anatomical structure at fault cannot be deduced, its recognition allows backache to be localised more accurately, and its treatment and progress to be assessed objectively This well-defined syndrome can easily be elicited in over 85% of cases which are usually described as torticollis, fibrositis, pleurodynia, myalgia, lumbago or sacroiliac strain, and in some cases of sciatica or coccydynia

I discovered this syndrome accidentally in 1953 when I had a nagging ache in the right sacroiliac region and noticed that my clothes felt rough and coarse over the affected area After manipulation without anæsthesia the ache, the tenderness, and the abnormal skin sensation disappeared within a few minutes The changes in skin sensation, which I now think arose from an area of hyperæsthesia, seemed so definite that I decided to follow up this chance observation by examining carefully all employees who came to our medical centre with acute backache I found such an area so often that I soon extended my researches to all cases of pain in the neck, shoulders, chest, loins, buttocks, and thighs

The Investigation

This article is based on 239 cases, which came to my notice among the 5400 employees of this engineering works, between September, 1953, and August, 1958, but only the first 100 are studied in close detail These were chosen alphabetically, and they were all re-examined in August, 1958 They were first seen as follows

Year	1953	1954	1955	1956	1957	1958
No of cases	1	4	15	22	33	25
			Total 100			

In many patients the symptoms started when they were away from work, and a twisting lift was the commonest cause (fig 1) Many of the other activities—e g, sport and gardening—which precipitated the syndrome also contain a large element of twisting Because the sharp pain at the onset of this syndrome is followed by a dull ache, patients tended to struggle with it for three or four days before going to the medical centre Many feared being put off work and did not consult their own doctors I saw 25 cases within twenty-four hours of onset, 56 within five days, and 19 on the fifth day or later

METHOD OF EXAMINATION

The patient stood or sat with his back to the examiner, and bare from the head to the gluteal fold The area of hyperæsthesia was found by drawing a pin (usually an open safety-pin) with medium pressure down the back about 2 in lateral to the midline, and at an angle of 45° to the surface The patient was asked to say when the pin became blunt or sharp as it moved down the back, the word "blunt" was always put before the word "sharp" When an area of change was reached the patient was asked to describe the new sensation The commonest expressions were "You're digging the pin more", "It feels sharp", and "It tickles", but occasionally the patients said it felt hot, or it hurt, or it was "just like an electric shock" They were then asked to say "yes" when the pin started to feel sharp, and *not* when it reached its maximum (many cases showed a distinct area of intense hyperæsthesia within the larger area of less severe hyperæsthesia)

The Hyperæsthesia

Fig 2(a) was made by superimposing and averaging all the hyperæsthetic areas During the past year I have seen several cases in which the hyperæsthesia really comprised two concentric areas, the outer being an area of "tickle", and the inner of extreme sensitivity to pin scratch (see case 75 and fig 3(a) These two areas of hyperæsthesia were easily distinguishable in the lumbar and sacral regions but not so readily (fig 2[a]) in the thoracic and cervical regions The hyperæsthetic areas extend downwards and outwards—i e, caudad and ventrad—from the

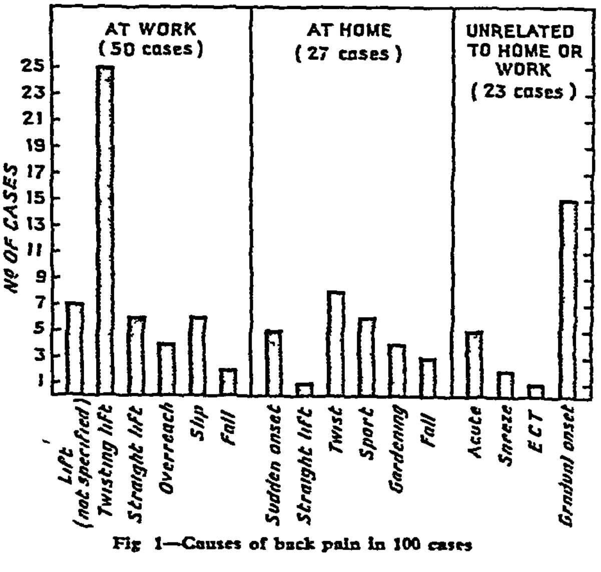

Fig 1—Causes of back pain in 100 cases

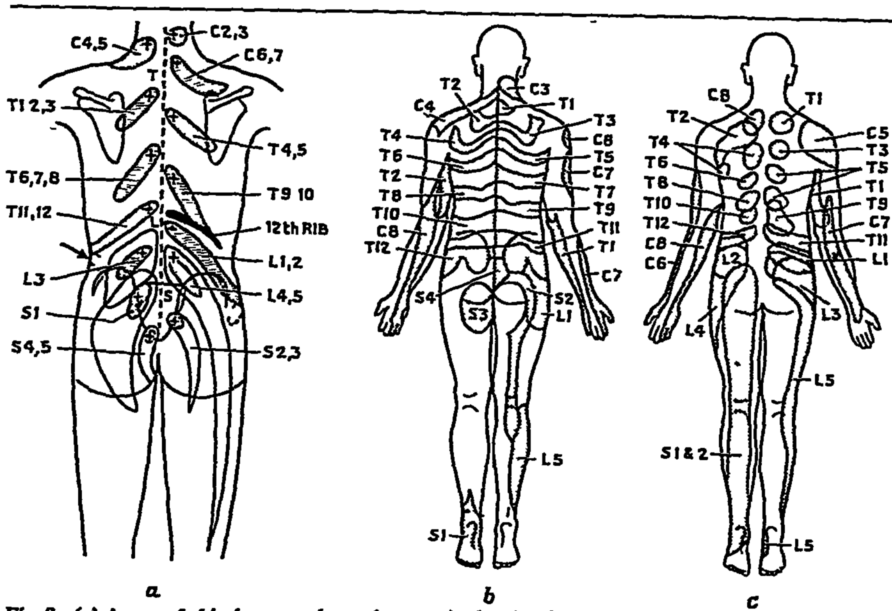

Fig 2—(a) Areas of skin hyperæsthesia (see text), showing inner and outer zones of acute sensitivity in the lumbar and sacral areas, (b) Head's dermatomes, and (c) Kellgren's areas of referred pain.

([b] and [c] are after Lewis 1942.)

paravertebral tender spots, but they rarely reach below the elbow or the knee-joint. The areas are bandlike in the thoracic region, and ovoid or rhomboid in the cervical, lumbar, and sacral regions. They do not reach the midline dorsally except occasionally in complete bilateral cases when they fuse in a narrow strip.

If the syndrome was not treated, or did not recover spontaneously, *the hyperæsthesia remained constant for* up to two or more years. If the outline was left on and the patient was re-examined next day, the edge was often accurate to within 2 mm., which is remarkable when one recalls that the lowest limit of two-point discrimination in the lumbar region is about 5 cm.

The Tender Spot

The force required by the examiner's thumb to elicit a tender spot within the hyperæsthetic area varied from slight pressure to the *heavy pressure required in certain* cases before the patient could decide which side was more tender. The tender spot was small, and the point of greatest tenderness was remarkably constant in relation to the spine, being nearly always more than $^1/_2$ in. yet rarely more than 2 in. lateral to the midline. Thus it lay over the line of the intervertebral synovial joints, the intertransverse ligaments, and the transverse processes of the vertebræ, and, lower down, over the line of the sacroiliac joints. Only in cases with bilateral symptoms was the tenderness occasionally greatest over the midline. In fig 2(a) these tender spots are marked with crosses.

The relation of the tender spots to the hyperæsthetic areas was also very constant, the spot being either just inside (74%) or just outside (26%) the superomedial limit of the hyperæsthesia. This was probably because in the early cases I often missed the outer area of tickle—i.e., *the* tender spot was inside the area of tickle but outside the area of sharpness.

Paravertebral tenderness is an essential sign in the syndrome. If tenderness is not present the back has probably righted itself, and the small area of hyperæsthesia is merely an afterglow.

The Dull Ache

The typical history is of a sharp pain lasting a few seconds at the time of the incident, which is followed half to two hours later by a nagging ache, felt deep in the tissues, and extremely difficult to localise. The aching pain is characteristically worse after sitting for a long time, and occasionally it is made worse on coughing.

The Limitation of Trunk Movement

In order to make the diagnosis, to assess the severity of the pain, and to watch the progress, all patients were asked to:

1. Bend forwards and then backwards (flexion and extension of the spine).
2. Bend to the right and to the left (lateral flexion).
3. With fingers linked behind the neck, to twist to the right and then to the left (rotation).

I noted whether any of these six movements was limited by pain, and also the approximate angle of forward flexion which was free of pain.

The only striking finding was the lack of pain in *14%* of cases on leaning backwards (i.e., spinal extension). I hoped that recording the limitation of spinal movements would give a clue to the structure at fault beneath the area of hyperæsthesia, but unfortunately it did not. There was no correlation, for example, between the segment involved and the movement which caused pain. Recording the range of movement was very useful in assessing the *subjective* improvement in pain after treatment. This corresponded closely with the objective disappearance of tenderness and hyperæsthesia.

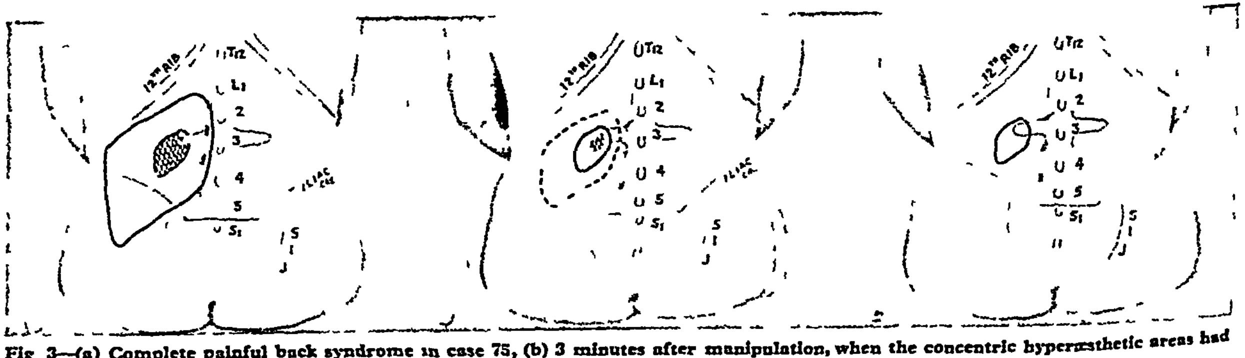

Fig 3—(a) Complete painful back syndrome in case 75, (b) 3 minutes after manipulation, when the concentric hyperæsthetic areas had shrunk. (c) area of hyperæsthesia remaining after 6 minutes.

THE SERIES

86 of the 100 cases studied in detail showed between them 132 examples of the complete syndrome. Of these, 58 patients had the single syndrome, 22 had the syndrome at two levels, 6 had it at three levels, and in 12 the syndrome had recurred Since the cause of the syndrome is unknown, bilateral cases (complete or incomplete) were regarded as single Of the remaining 14 cases, 4 had all the features of the syndrome except hyperæsthesia, and they were improved by manipulation, 5 had generalised aching of muscles with no features of the syndrome, and they all improved gradually, 4 had been cured before I examined them by manipulation under anæsthetic, retraction, radiant heat, or a plaster jacket, and 1 case was a disc syndrome which was relieved by operation

In table I the cases are grouped according to vertebral regions, and each region is divided by its number of vertebræ to obtain the frequency for each vertebral segment

TABLE I

Region	No of syndromes	No of vertebræ in region	Segmental frequency	Recurrences
Cervical	7 (5%)	7	1	0
Thoracic	33 (25%)	12	2 75	3
Lumbar	38 (29%)	5	7·6	2
Sacral	54 (41%)	5	10 8	7
Coccygeal		4		

Table I shows that the lower segments of the spine are more often affected than the upper, and that the frequency increases steadily from the neck to the sacrum. Pain over the sacral segments is probably referred from the sacroiliac joints, and, even if the sacrum is regarded as five fused joints, the sacral region is still the commonest site of this syndrome I have seen 1 coccygeal case, caused by a fall into the sitting position, but this was not among the first 100 cases studied

Complete bilateral syndromes (i e, with a tender spot on either side of the midline and with two accompanying areas of hyperæsthesia at the same segmental level) arose in 12% of cases, and incomplete bilateral syndromes (i e, an area of hyperæsthesia with its tender spot on one side of the midline, and an area of hyperæsthesia without a tender spot on the other side) in 17% (table II)

TREATMENT

All cases except those involving the cervical region were manipulated unless there were contraindications or the patient was being treated by another doctor Manipulation of the thoracic region was by rotation (with the patient sitting with his hands behind his neck), for the lumbar and sacral regions the spine was rotated with the patient lying in the Sims' position, with the affected side uppermost After successful manipulation the tenderness disappeared at once, the hyperæsthesia diminished, the dull ache was relieved, and the range of spinal movement became full

Of the 132 examples of the syndrome 97 (73%) were manipulated, of these manipulations 86 (89%) were successful In 67 (78%) of the cases with a successful outcome a definite click was associated with the manipulation. The clicks during manipulation of the thoracic and lumbar regions correspond in time to the coarse noise heard during sacroiliac manipulation

TABLE II

Region	Complete bilateral	Incomplete bilateral	Total
Cervical	1	0	1
Thoracic	5	6	11
Lumbar	4	4	8
Sacral	6	11	17
Total	16	21	37

I did not attempt to treat a control group in any other way—with infra-red heat only, for example The syndrome may disappear spontaneously, either suddenly during an unusual movement, such as a stretching yawn or a twisting step down, or gradually over days or weeks Hence manipulation may not be the best treatment in all cases, nor the treatment of choice in the first instance.

After manipulation in 12 cases an identical syndrome recurred in the same segment, and in each of these gave a history of a second traumatic incident—e.g, a lift or an accident. The time-interval varied from a week to two years, the average being six months

ILLUSTRATIVE CASE-REPORTS

Case 75—A costing clerk, aged 25, played hockey one Saturday afternoon, and next day had a severe ache in his left loin After two nights of pain, which he had tried to relieve with liniment and hot water bottles, he came to the medical centre.

Though he was not in severe pain when standing, all his movements were apprehensive. His range of movement was as follows

	Right	*Left*		
Bending	—	+	Forwards	45
Twisting	—	—	Backwards	—

He had an ache down his left leg, which was increased by straight-leg raising, Lasegue's test increased the ache, but did not cause sharp sciatic pain The knee and ankle jerks were normal No areas of anæsthesia were found on the legs or lower trunk. Fig 3(a) shows the outline of the two areas of hyperæsthesia, and the tender spot is marked with a white cross

As the patient was put into position for manipulation, lying on his right side, he had pain in the cross-hatched area During manipulation, which comprised one firm push on the left iliac crest, a click was heard. He could then immediately touch his toes, and the tenderness had gone Within two minutes the areas of hyperæsthesia had shrunk as shown in fig 3(b), after five minutes it had diminished as in fig 3(c), and in ten minutes there was no sign Spinal flexion was now pain-free

Next day he had no tenderness or hyperæsthesia A month later all spinal movements were full, and he had no abnormal physical signs

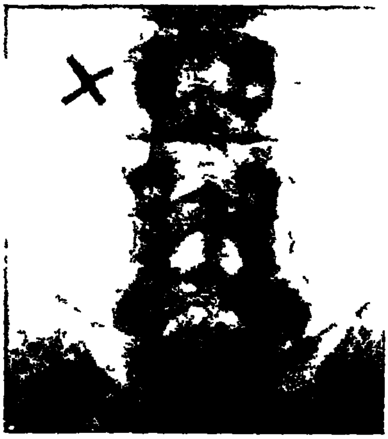

Fig 4—Radiograph of case 75 showing relation of maximum paravertebral tenderness over the left transverse process of L3.

Radiography before manipulation showed that the tenderness was not over the small intervertebral synovial joint but over the outer half of the third left lumbar transverse process (fig 4)

Case 57—A storeman, aged 23, was lifting brackets in trays, each weighing 60 lb and twisting with them to the left, when he suddenly got pain over the sacral region. He had never had any back trouble previously

I saw him within an hour of the damaging lift His leg reflexes were normal, and no area of anæsthesia was found His movements were limited thus

	Right	*Left*		
Bending	+	+	Forwards	<20°
Twisting	+	+	Backwards	+

He had a considerable area of hyperæsthesia over his right buttock, and a tender spot between the L5 spine and posterior-superior iliac spine, and a lower tender spot on the sacroiliac joint line on the same side Thus there were two syndromes with a fused area of hyperæsthesia After manipulation, the lower tender spot disappeared, the hyperæsthetic area shrank, and the pain eased considerably

Next day there was still a slight L5 syndrome His back was therefore manipulated again, when a second click was heard The hyperæsthesia disappeared in five minutes, and next day the patient had no signs or symptoms Seven months later he had had no trouble since the last manipulation All movements were pain-free, but there was still an area of hyperæsthesia without a tender spot over the right buttock

This case illustrates that pain in the back may be due to two contiguous syndromes, each of which needs a separate manipulation

A Syndrome in Other Joints

I have also found a similar syndrome over the elbow (both radiohumeral and ulnohumeral), 1st metacarpo-phalangeal, acromioclavicular, and knee joints When areas of hyperæsthesia were discovered over the small bones of the wrist and ankle, it was impossible to say which joint was involved

In these peripheral joints the syndrome comprised

1 An area of hyperæsthesia surrounding a tender spot and extending above and below the joint
2 A tender spot on the line of the joint
3 A dull ache, difficult to localise, but usually extending below the joint
4 Limitation of range of at least one movement of the joint by pain

These four features correspond closely to those of the back syndrome It is important to note that the involved joints were all peripheral synovial joints with capsules

Discussion

Henry Head (1893, 1894) studied areas of hyperæsthesia and worked out their relation to ventrally placed pathological processes, such as acute sinusitis, dental infections, engorged breasts, cholecystitis, gastric ulcers, and appendicitis He also worked out the dermatomes of the central nervous system (fig 2[b]), but he was never able to fit the areas of hyperæsthesia into the neurological dermatomes James Mackenzie (1892) used the ventral areas of hyperæsthesia extensively in his clinical work, but he differed from Head in declaring that tenderness over a diseased organ was referred to the muscles of that segment and was not due to increased sensitivity of the inflamed tissues of the organ itself If this is so the paravertebral tender spots in the painful back syndrome may well result from referred tenderness in muscle overlying some structure, such as a joint or ligament, which is the real seat of trouble, it is wrong to assume that a tender structure is necessarily the cause of the syndrome The hyperæsthetic areas in my patients seem to correspond more closely to Kellgren's areas of referred pain (Kellgren 1939), and to the sclerotomes of Inman and Saunders (1944), than to the dermatomes of Head (1893), Sherrington (1893), and Foerster (1933) Hence I think these areas of hyperæsthesia should be regarded as the skin component of the sclerotome The dermatomes were mapped out in direct relation to nerve-roots in cases of herpes zoster (Head 1893), and by division of the nerve-roots in monkeys (Sherrington 1893) and in cases of nerve-root resection (Foerster 1933), whereas the sclerotomes were worked out in volunteers in terms of deep referred pain from injection of interspinous ligaments with hypertonic saline (Kellgren 1939) or from direct physical or chemical stimulation of deep mesodermal tissues (Inman and Saunders 1944) Inman and Saunders say that " the physician, on examination of skin sensation, is unable to discern anything of an objective nature except perhaps occasionally a slight hyperalgesia " Though in early papers the terms hyperæsthesia and hyperalgesia are used indiscriminately, I prefer to reserve " hyperalgesia " for a painful response to skin stimulation and " hyperæsthesia " for an increased sensitivity of the skin without pain (Lewis 1942)

What Causes this Syndrome?

The painful back syndrome, which is an everyday occurrence, in my view represents a disturbance of a mesodermal structure It is not caused by damage to ectodermal tissues (i e, the skin or the spinal or peripheral nerves), if it were one would expect signs after months or years of nerve compression—a patch of anæsthesia or paræsthesia in the corresponding dermatome, and muscle wasting or diminished limb reflexes Nor is it caused by true endodermal structures (i e, the actual mucous membrane of the gut) for these are insensitive to stimuli

In descending order of likelihood, the following mesodermal structures may cause this syndrome joint capsule, synovial membrane of the joint, ligaments, ligamentum flavum, fascia, muscles, tendons, blood-vessels, intervertebral disc, periosteum, bones, cartilage, fat, and the large specialised organs As the syndrome is closely associated with the spine yet also arises in peripheral synovial joints, such as the elbow and knee, it is reasonable to suggest that the synovial joints of the spine (i e, the intervertebral synovial joints, and the sacroiliac joints) are causally related During manipulation the spine is fully rotated, and at the extreme limit of rotation an extra jerk is needed to produce the click which occurs in over 75% of cases

The structure at fault is, I think, intimately connected with the small intervertebral synovial joints, either a ligament is under tension, or the synovial membrane (or capsule) of the joint has become nipped The synovial membrane or capsule may be nipped on recoil when the joint has opened beyond its normal range, and this would cause local tenderness, dull ache, referred hyperæsthesia, and possibly protective muscle-spasm around the joint

If an articulated spine is rotated the synovial joints open up all down one side and close on the other If a thick elastic band is then placed between the transverse process of one vertebra and the spine of the vertebra above—e g, from the left transverse process of L3 to the spine of L2—and the spine is rotated as though it were being manipulated, the facets all down the left side separate except those between L2 and L3 A last jerk is needed to overcome the elastic band (representing the muscles in spasm guarding the joint) before this joint opens and then snaps shut again with a click The click is similar to that produced in certain people by cracking the metacarpo-phalangeal joint, and this is thought to be due to a bubble of nitrogen suddenly forming in the synovial fluid (Roston and Haines 1947)

The synovial membrane or capsule could only be nipped by some unusual movement, such as excessive rotation One of the functions of the elastic ligamentum flavum, which is attached to the medial edge of the capsule of each spinal synovial joint, is to prevent the capsule from being caught in the joint (Badgley 1941), and at manipulation the ligamentum flavum would, by elastic recoil, pull the nipped capsule free But this is only theory I have been unable to demonstrate the opening of the spinal facets under the X-ray screen or on radiographs taken before and after manipulation, because the synovial membrane is less than a thousandth of an inch thick, and in the living spine cartilage fills most of the space of these joints

Because visceral disease can give rise not only to ventral and dorsal areas of hyperæsthesia but also to tenderness of the vertebral spines (Mackenzie 1918), the back syndrome is only complete if at least one spinal movement is limited by pain in the back In acute cases with a graphic history of an incident precipitating pain, one can treat the patient with an incomplete syndrome, but in cases which evolve gradually over days or weeks demonstration of the complete syndrome is of diagnostic and localising value

Relation to the Prolapsed Intervertebral Disc

The painful back syndrome can appear and disappear without the symptoms or signs of a prolapsed intervertebral disc Pain is the only symptom common to each syndrome, but the two types of pain are distinguishable With a chronic disc lesion the pain is lancinating or like a red-hot needle, and it may often follow the course of a nerve In the painful back syndrome the pain is a dull ache, which is less extensive but more diffuse

Summary

A syndrome of back pain is described, comprising (1) skin hyperæsthesia, associated with (2) a tender spot, (3) a dull ache, and (4) limitation of spinal movement by pain

100 cases of this syndrome were studied in detail, in 86 of them 132 areas of hyperæsthesia were found, and these areas followed the sclerotomes rather than the dermatomes

After one successful manipulation, the syndrome usually disappeared within a few minutes

The hyperæsthesia is thought to be the skin component of pain arising in deep mesodermal structures The syndrome may be due to nipping of the synovial membrane between the interarticular facets or the sacroiliac joint, or to tension of a joint ligament In either case manipulation restores the normal function of the joints

I should like to record my thanks to Dr G Laurence, my predecessor, to Miss S D Chard, Sister R E Parks, and the nurses, for help with these patients, to Mrs B D Bird for the typing, to Mr L H Payne, works photographer, for the photographs, to Mr N G Cadman, director and works manager, for encouragement in this work, and to Mr M W Shorter, managing director, for permission to publish this paper and also to Dr H J Johnson, radiologist to the Royal United Hospitals, Bath, for the radiograph

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TWO EPISODES OF ACUTE RENAL FAILURE WITH COMPLETE RECOVERY OF RENAL FUNCTION

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In the past ten years there have been many reports of cases of acute renal failure treated either conservatively or by dialysis with an artificial kidney (Alwall et al 1955, Kolff 1955, Palmer et al 1957, Parsons and McCracken 1958, Bluemle et al 1959, Schulz and Murphy 1959, Skouby 1959)

To our knowledge only 1 case has been reported in which there were two separate episodes of acute renal failure (Bluemle et al 1959), and this patient died during the second episode

The present case is probably the first recorded one in which the patient survived two separate episodes of acute renal failure and was subsequently found to have normal renal function

Case-report

First Episode

A 21-year-old woman was admitted to the Auckland Hospital on Sept 15, 1956, following postpartum hæmorrhage There was no past history of renal disease or urinary tract infection, but one year previously she had been delivered of a stillborn baby after antepartum hæmorrhage for which she required a blood-transfusion of 6 pints The second pregnancy was normal, as was the delivery of a healthy baby on Sept 13, 1956, but the postpartum hæmorrhage caused shock and hypotension (blood-pressure 60/40 mm Hg) for which she was given a transfusion of 3 pints of blood (Group-O rhesus-negative) On the day after delivery she vomited several times, and oliguria developed

On admission the patient was in good general condition with a blood-pressure of 110/60, there was no sacral or ankle œdema, and she appeared adequately hydrated

Investigations —Hb 13 6 g per 100 ml, direct Coombs test negative, blood-non-protein-nitrogen 74 mg per 100 ml, serum-sodium 121 mEq per litre, serum-potassium 5 3 mEq per litre, plasma-chloride 93 mEq per litre, plasma-bicarbonate 19 6 mEq per litre, serum-bilirubin 0 8 mg per 100 ml, serum-protein 5 6 g (albumin 2 3 g, globulin 3 3 g) per 100 ml Electrocardiogram complete heart-block with normal T waves Chest X-ray normal

Treatment and progress —The patient was treated conservatively with diet containing 1500 calories, a minimal protein intake, and a fluid intake restricted to obtain a daily positive balance of 750 ml The progress of this episode of acute renal failure is indicated in fig 1 The oliguria lasted nine days, the serum-potassium rose to a peak of 7 55 mEq per litre, and the blood-non-protein-nitrogen to a maximum of 215 mg per 100 ml

During the period of oliguria the patient became nauseated, vomited, and was given chlorpromazine Nine days later she became mildly jaundiced, the jaundice cleared rapidly after withdrawal of chlorpromazine

The patient had satisfactory diuresis, and on discharge after thirty-one days in hospital her blood-non-protein-nitrogen was 22 mg per 100 ml

The total atrioventricular dissociation persisted, and this was considered to be an unrelated congenital heart-block. While in hospital the patient required transfusion with 5 pints of blood to maintain her hæmoglobin, which on discharge was 13 6 g per 100 ml. During this last week in hospital recurrent boils developed

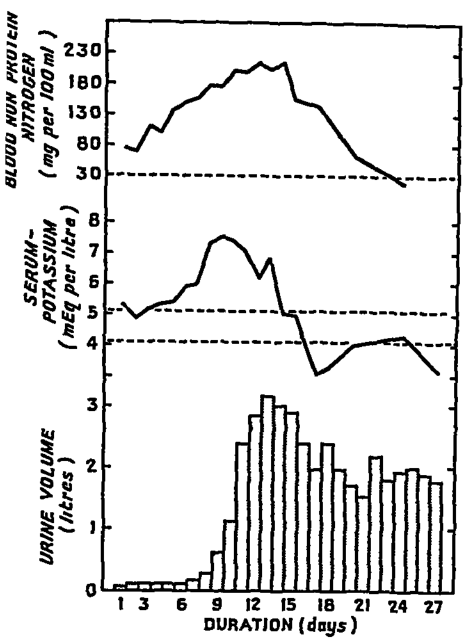

Fig 1

Fig 1—First episode of acute renal failure blood-non-protein-nitrogen, serum-potassium, and urine volume

Fig 2—Second episode of acute renal failure blood-non-protein-nitrogen, serum-potassium, and urine volume

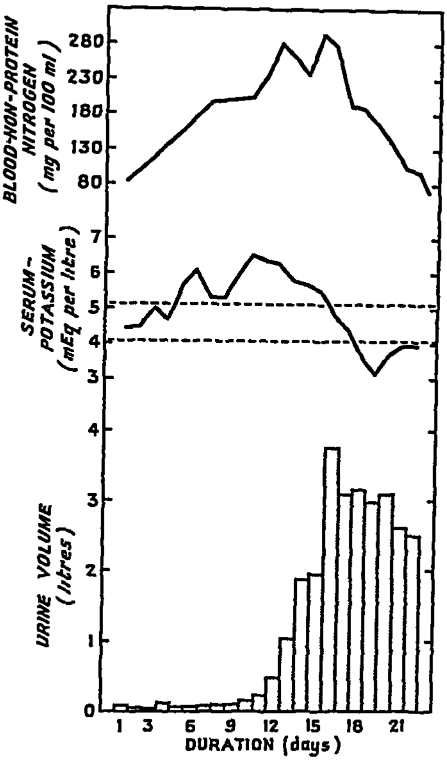

Fig 2

At subsequent follow-up the patient was in good health with a normal blood-non-protein-nitrogen The complete atrioventricular dissociation persisted

Second Episode

The patient was again admitted to Auckland Hospital nine months later on May 1, 1957, with severe oliguria She had been well until two days previously when she was admitted to another hospital for elective tubal ligation The operation had been uneventful and the patient had not appeared shocked There was no record of her blood-pressure during the postoperative period, but twenty-four hours later her urine output dropped

On account of vomiting she was given one injection of chlorpromazine, and within twelve hours she became jaundiced

On admission her blood-pressure was 96/50 and pulse-rate 120 per minute, she appeared drowsy, jaundiced, and dehydrated, there were no other significant abnormalities on examination

Investigations—Hb 9 9 g per 100 ml , white-blood cells 7100 per c mm (differential count normal), direct Coombs test negative, red-cell osmotic fragility test normal, no fœtal hæmoglobin detected, fibrinogen screen test normal, bone-marrow, normal maturation of both red and white cell precursors Blood-non-protein-nitrogen 84 mg per 100 ml , serum-sodium 124 mEq per litre, serum-potassium 4 4 mEq per litre, plasma-chloride 98 mEq per litre, serum-bilirubin 5 5 mg per 100 ml , serum-protein 5 7 g (albumin 3 0 g , globulin 2 7 g) per 100 ml , colloidal gold 0, thymol turbidity 1 8 units, zinc sulphate 6 4 units, serum-alkaline-phosphatase 14 0 King-Armstrong units Electrocardiogram complete heart-block with normal T waves

Treatment and progress—During this second episode the patient was treated conservatively with 50% glucose and vitamins given by intravenous polyethylene catheter into the superior vena cava The fluid balance was maintained with a positive balance of 550 ml , and the oliguric phase lasted twelve days (see fig 2) Again the patient had hyperkalæmia with a peak of 6 5 mEq per litre, and the blood-non-protein-nitrogen rose to a maximum of 295 mg per 100 ml The patient was given insulin in the drip for period when the serum-pot sium level was raised

The jaundice, with a seru bilirubin of 5 5 mg per 100 n on admission, subsided and t serum-bilirubin was norm within five days The patie required transfusion of fo pints to maintain her hæm globin, and on discharge aft thirty-six days in hospital blood-non-protein-nitrog was 30 mg per 100 ml

Reassessment

In the thirty months after t second admission with acu renal failure the patient mained well with no urin symptoms or recurrence jaundice When admitted reassessment at the end of t time, the blood-pressure w 110/80 and physical examir tion was unremarkable

Renal function tests—Urı no protein, no sugar, mic scopy normal, no bacter growth Blood-urea 17 mg 100 ml , serum-creatinine mg per 100 ml , creatinı clearance test 99 ml per mi specific gravity concentrati and dilution test 1024 and 1000 respectively, glomeru filtration-rate (inulin-clearance test) 124 ml per min , re plasma-flow (*p*-aminohippuric-acid-clearance test) 790 per min

Discussion

The first episode of acute renal failure was due hypotension as a result of postpartum hæmorrhage, t the cause of the second incident is less definite probably resulted from postoperative hypotension, blood-transfusion was not given until renal failure w established, and investigation revealed no evidence hæmolytic anæmia

Jaundice did not develop on the first admission duri the early period, and was only evident two weeks after t patient's admission to hospital, on the second occasi jaundice was present at the time of admission The ti sequence in relation to the chlorpromazine therapy consistent with this drug being the cause of the jaundi (Meyler 1958, Hollister 1957)

Finkenstaedt and Merrill (1956) showed some eviden of impaired renal plasma-flow or glomerular filtration-r in 13 out of 16 cases studied three to seventy-six mont after a single episode of acute renal failure, but in only 1 these 16 patients was the specific gravity concentrati test still impaired A second incident of acute rer failure must be very rare as only 1 instance has be recorded (Bluemle et al 1959), and therefore one episo does not appear to predispose to further attacks, but in t present case the shock which precipitated the secon episode appeared comparatively trivial

We wish to thank Dr B Quin, under whose care this patient w originally admitted, Dr J M Staveley for the hæmatologi investigations, and Dr F Sims and Dr R Howie for assistan with the renal function tests

References at foot of next column

INTERMITTENT POSSIBLY FAMILIAL INTRAHEPATIC CHOLESTATIC JAUNDICE

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IN recent years several new syndromes of jaundice have been recognised, some of which are thought to be due to inborn errors of metabolism (Meulengracht 1947, Crigler-Najjar 1952, Dubin 1958). Furthermore a number of cases of chronic cholestatic jaundice, probably belonging to the same group of diseases, have been described (Rotor et al 1948, Stransky 1950, Schiff et al 1959, Davis and Young 1959, Haverback and Wirtschafter 1959, Summerskill and Walshe 1959), but the cases have been too few for syndromes to be clearly defined.

At an interval of one year two boys, each 15 years of age, were examined at Rigshospitalet, Copenhagen, on account of intermittent jaundice since early childhood. They belonged to the same small community (9000 inhabitants) in the Faroe Islands, and claimed to be related to each other, although the nature of their relationship could not be established. There were no other known cases of jaundice in that particular island when jaundice appeared in the boys, there were no familial cases apart from these two, and neither patient had had neonatal jaundice.

Case-records

Case 1 had had attacks of jaundice, lasting two to three months, at the age of 2 and 4 years. He was then well until the age of 12, when jaundice recurred and laparotomy was performed. No gross abnormality of liver or bileducts was found (no biopsy or cholangiography), but cholecystogastrostomy was undertaken. Two months later jaundice disappeared, but three years later it recurred after an attack of Asian influenza. On admission to Rigshospitalet the patient felt tired, had poor appetite, and was losing weight. Skin and scleræ were much jaundiced, there was no hepatosplenomegaly, spider nævi, ascites, or œdema. The laboratory findings are shown in the accompanying table.

LABORATORY DATA

Test	Case 1	Case 2
Serum-bilirubin (mg per 100 ml)	34·8	14·9
% direct reaction, 10 min	Not done	85
Serum-alkaline-phosphatase (K.A units)	94	49
*Thymol turbidity**	0·04	0·02
S.G.O.T.	6·0	3·4
S.G.P.T.	1·0	11·0
Eosinophils (per µl)	40	500
Serum-potassium (mEq per litre)	2·8	4·0
Serum-cholesterol		
Total (mg per 100 ml)	234	386
Free (%)	62	29
Fæcal fat (g per 24 hr)	48	14
Serum-albumin (g per 100 ml)	3·1	3·1
Serum-α-globulin (g per 100 ml)	1·5	1·0
Serum-β-globulin (g per 100 ml)	1·5	1·5
Serum-γ-globulin (g per 100 ml)	0·7	1·0
Urine-bilirubin	+++	Not done
Urine-urobilinogen	Neg	Not done
Oral and intravenous cholecystography	Not displayed	Not displayed
Ghedini-Weinberg and Casoni test †	Not done	Neg
Toxoplasma complement-fixation test	Not done	Neg

* Extinction units normally less than 0·14. † Echinococcus test.
S.G.O.T.=serum-glutamic-oxalacetic-transaminase. Normally less than 1·7 units.
S.G.P.T.=serum-glutamic-pyruvic-transaminase. Normally less than 1·6 units.

As biliary obstruction, possibly a late result of the cholecystogastrostomia, was suspected, the patient was operated on again. No obstruction was visible, operative cholangiography was normal, and the liver appeared normal apart from the jaundice. The gallbladder was removed on account of chronic inflammatory changes at the site of the anastomosis, and a liver biopsy was taken. The biopsy specimen showed slight periportal fibrosis and moderate infiltration with mononuclear cells and granulocytes, including a few eosinophils. Many of the bile canaliculi were distended with bile, and many liver cells contained much bile pigment (but no other detectable pigment), there was no necrosis. The postoperative course was complicated by long-continued suppuration, but eventually the wound healed and jaundice gradually disappeared, the serum-bilirubin level being normal when he left the hospital three months after the operation. A year later he was reported to be well.

Case 2 had been jaundiced with remarkable regularity for two to three months at a time, with free intervals of the same duration, from the age of 1 to the age of 7 years. At laparotomy when he was 6 years of age the liver and biliary tracts were macroscopically normal (no biopsy or cholangiography).

Between the age of 7 and 15 he had no jaundice and developed normally. Then he had a further attack, and after two months was admitted to Rigshospitalet. The findings were essentially the same as in the first patient. Furthermore this patient was found to be allergic to eggs and milk, and the peripheral blood contained slightly increased numbers of eosinophils. Although the patient recalled no coincidence of his allergic manifestations (vomiting and diarrhœa) and the periods of jaundice, the cause of the jaundice was thought to be possibly allergic. Therefore prednisone 40 mg daily was given for three weeks, but the serum-bilirubin level was unchanged, and he returned to the Faroe Islands unimproved. Four months later, according to his doctor, his condition had deteriorated and he was still losing weight, but after a further two months his condition was improving, jaundice and itching had disappeared, and he was able to continue school after an interruption of more than six months.

Discussion

From the clinical, biochemical, and histological findings it must be concluded that in these two cases the jaundice was due to intermittent intrahepatic cholestasis. The most common causes of intrahepatic cholestasis—viral hepatitis and certain drugs—can be ruled out in the present cases. The most likely mechanism is some defect in the excretion of bilirubin by the liver cells, similar to that suggested by Dubin (1959) in chronic idiopathic jaundice (Dubin-Johnson syndrome), or an allergic "cholangiolitis" (which is supposed to be the cause of chlorpromazine jaundice), but the nature and the site of the lesion in intrahepatic cholestatic jaundice remains obscure (Popper and Szanto 1956).

The cases described by Rotor et al (1948), Stransky (1950), Schiff et al (1959), Davis and Young (1959), and Haverback and Wirtschafter (1959) probably belong to one group, differing from the present cases in being more constantly, though not so deeply jaundiced, and in having an histologically normal liver, normal liver-function tests (including serum-alkaline-phosphatase), and normal appearance of the gallbladder at oral cholecystography, but the difference may be merely quantitative. The two cases described by Summerskill and Walshe (1959) correspond closely to the present ones except that in these the jaundice first appeared much earlier, the patients were probably related, indicating a hereditary factor, and the patients' general condition was much affected during the

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periods of jaundice The failure of prednisone to reduce the serum-bilirubin level in case 2 suggests that the cause is not allergic, but possibly steroid hormones might have been effective at an earlier stage

Like Summerskill and Walshe we regard the disease as benign, for no signs of irreversible damage to the liver were found despite the severe and long-continued cholestasis Nevertheless the loss of weight, gross steatorrhœa, increased levels of serum-transaminases, and, in case 1, hypopotassæmia (see table), indicate that the condition may not be as harmless as other syndromes of constitutional hyperbilirubinæmia—for instance, the Gilbert-Meulengracht and Dubin-Johnson syndromes

Summary

In two cases intermittent jaundice first appeared at the age of 1 and 2 years The two patients belonged to the same small community in the Faroe Islands, and were probably related

Examination, including laparotomy with biopsy of the liver and direct cholangiography in one case, indicated intrahepatic cholestasis The symptoms were severe during the periods of jaundice, but the condition seemed to be completely reversible

My thanks are due to Prof K Brochner-Mortensen, medical department A, Rigshospitalet, for permission to report case 2, and to Chief-Surgeon E Andreassen, surgical department D, Rigshospitalet, for permission to report the findings at operation in case 1

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New Inventions

A DEVICE FOR THE IDENTIFICATION OF MICROORGANISMS

A SIMPLE means of identifying microorganisms would be welcomed both by the student and the more experienced microbiologist We have developed a device which, with suitable tables, makes identification of bacteria easier Its use could be extended to other kinds of microorganism

Principle

The main diagnostic characters of different organisms are recorded in columns on a " diagnostic table " The characters of the unknown strains are written (by grease pencil) in the same sequence in columns on a 'Perspex' plate Table and plate are aligned and the plate is moved from left to right over the table until the characters of a column on the plate are found to correspond to one of those on the diagnostic table A movable mask on the plate is used to isolate each column in turn and so facilitates recognition of similar patterns on plate and table

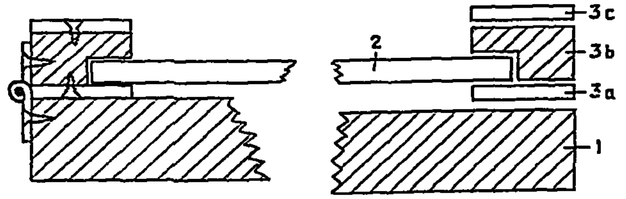

Fig 1—Diagram to show construction of determinator Right side is exploded

Description of Device

The essential features are shown in figs 1 and 2

(1) A baseboard, in our case $^7/_8$-in block-board

(2) A sheet of perspex, $^3/_{16}$-in thick Columns are drawn on the under surface by scribing at $^1/$-in intervals

(3) Guides for the perspex sheet formed by (a) brass strip, $^1/_2$-in thick, on which the perspex slides, (b) L-shaped wood strip, and (c) brass strip

The two sides formed by 3a, b, and c are joined by brass angle below which the perspex can be moved freely One side is attached to the base (1) by brass hinges, so that (2) and (3) form a hinged lid

A mask (4) is made of $^3/_{16}$-in perspex to which are fastened two brass strips with a gap $^1/_2$-in between them Two brass locating screws fit into holes (5) drilled in the perspex plate at $^1/_2$-in intervals

Diagnostic tables of up to 25 characters are made on $^1/_4$-in squared foolscap paper A guide line is drawn $^1/_2$-in below one edge of the long (13-in) side Names of characters are listed on the left side of the paper, and the actual characters of the different organisms are recorded in alternate columns by appropriate letters (e g, R for rod, S for sphere) or signs (+, —,)

A simple example, using IMVIC reactions for three species (A=*Escherichia coli*, B=*Citrobacter freundii*, C=*Aerobacter aerogenes*) is shown here and in the illustration

	A	B	C
Indole	+	−	−
M R	+	+	−
V-P	−	−	+
Citrate		+	+

To use the device, the lid is lifted and the diagnostic table placed on the base so that the guide line will be in register with the brass strip on the hinge side of the lid

The results of tests are scored in grease-pencil on the perspex sheet, putting the markings to the right of each scribed column Each culture is labelled by a serial number written at the head of the column When all the results have been " written up " on the perspex, the mask is put on so that the experimental results of one column at a time are visible, and the perspex sheet is moved over the different diagnostic columns until the best match is found The code letter of the diagnostic table indicates the identity of the organism

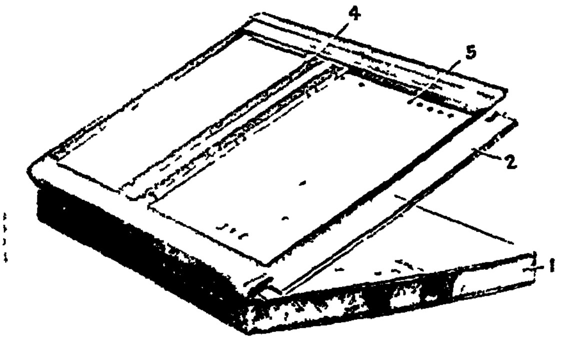

Fig 2—Determinator in half-open position for insertion of the diagnostic table Holes in the perspex plate are for the locating screws of the mask.

Discussion

The usefulness of the device will depend on the diagnostic tables A table can be prepared for the allocation of an unknown organism to a major subdivision (we use the word "set", to avoid "group" which has special meanings in bacterial taxonomy), by the use of other and more detailed tables, a further pinpointing of the identification can be made Specialist workers will not need the general type of table that would be useful to a student An example of a specialised table that could be used by one dealing with enteric bacteria is table 1 of a paper by Cowan [1]

Since our device forms a useful supplement to *Bergey's Manual of Determinative Bacteriology*,[2] we call it a Determinator

We wish to thank Dr O M Lidwell and Mr S P Clark for help in designing and constructing the device, and Mr W Clifford for the photograph

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THE ILIACOMETER

With the accepted method of measuring the length of a leg, the patient is recumbent, but in my view it is the "operative" or upright length of the leg which is important, except in cases of suspected fracture This is especially so when minor degrees of shortening may be responsible for scoliosis

"Idiopathic" (and so-called "adolescent") scoliosis are often caused by tilting of the pelvis due to a short leg The iliac crest is therefore the indicator and the length from this point to the ground is the operative length of the leg

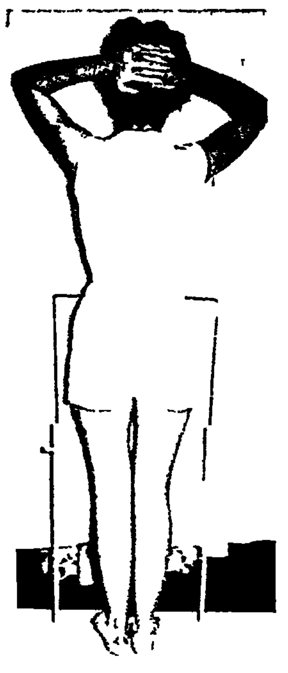

Fig 1—The iliacometer in use (normally the shorts would be turned down)

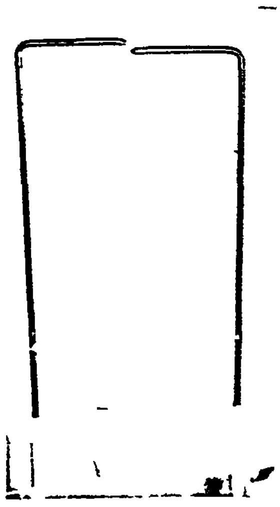

Fig 2—Reading of iliacometer

The iliacometer is used as follows

The patient stands barefooted on a level surface (fig 1), a sheet of 'Masonite' (hardboard) The highest point of the iliac crest is marked with a skin pencil or ball-point pen, the tips of the angled rods are then adjusted to these marks The rods slide in tubes attached to heavy bases and can be locked in position The patient then steps out, the points of the rods are brought together by moving the bases inwards and the difference in leg length becomes obvious (fig 2)

An appropriate leather and sponge rubber 'heel-raiser" can then be inserted in the shoe of the shorter leg

Philip H Dalgleish
M B Edin

Hillcrest Natal

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[1] Cowan S T *J gen Microbiol* 1956 15 345

[2] Bergey's Manual of Determinative Bacteriology (edited by R S Breed, E G D Murray, and N R Smith) London, 1957

Reviews of Books

The Future of Man

The Reith Lectures, 1959 P B Medawar, F.R S London Methuen 1960 Pp 128 10*s* 6*d*

The average listener to the Reith Lectures has probably no idea what a severe academic test they represent for the lecturer he is supposed to address the "average listener", but in the knowledge that all his heaviest professional colleagues are also listening The temptation in these circumstances to aim for generalities must be overwhelming, but Professor Medawar's series on the application of biology to human affairs, and its inapplicability to most of the matters it is most enthusiastically used to predict, is exemplary in avoiding them The lecturer who tries, as he has done, to give a series of real substance, finds himself riding a kind of expository Grand National in the circuit of this particular course, Professor Medawar has to explain to a lay audience the idea of overdominance in the genetics of human intelligence, of social communication as a second-order, Lamarkian "heredity" in man, and of linear senescence in orthoclones—to take three of the jumps at random. He remains in the saddle with the aplomb of a seasoned gentleman rider at the end, his audience has been genuinely instructed, and if it has not also been interested it ought to have been—while some of his professional colleagues will have learned a thing or two on the way, not least about the expression of scientific ideas in agreeable English, which runs as well on paper as it did at the first hearing

The Triumph of Surgery

Jürgen Thorwald London Thames & Hudson 1960 Pp 483 25*s*

When *The Century of the Surgeon* was published three years ago it was apparent that its author had discovered a new and highly successful method of writing medical history He had selected a series of important events—such as the first demonstration of anæsthesia in this country—and, by a painstaking study of contemporary records, had collected as much detailed information about them as possible They were then presented as the first-hand accounts of a hypothetical character, and linked by the story of his travels from one surgical centre to another An authority was quoted for virtually every statement made, and when the description of the episode already mentioned began "Monday, December 21st, 1846, was a bitterly cold day", it was because Liston himself had recorded as much

This volume begins where the first ceased, and Mr Thorwald now manipulates his imaginary eye-witness amongst the surgical giants of the years between 1880 and the first world war Because he has had a greater abundance of material on which to base his work, the book is even more convincing and exciting than its predecessors Even specialists on some of the topics discussed are unlikely to be familiar with all the information he has elicited (Few histories of thyroidectomy mention that at one time, before the invention of local anæsthetics, some surgeons were so perturbed by the incidence of laryngeal paralysis that they discarded anæsthetics altogether, and relied upon the protests of their conscious subjects to warn them when the nerves were in jeopardy)

It is a pity that in one instance, when describing the fatal illness of the Crown Prince Frederick, the author's usual objective style has been forsaken He exhibits a strongly partisan feeling for the German surgeons, and portrays Sir Morell Mackenzie as a querulous and incompetent character Nothing in such a portrait explains the great faith in him which his Royal patient and the Princess Victoria showed right up to the end of the whole tragic episode Nor is there any reference to the suggestion, which has since been advanced, that Mackenzie's management of the case derived from his suspicion that Frederick was suffering from another disease—that one which could not, by any convention, be named before or after the patient's death It must be admitted, however, the harsh judgment on Mackenzie notwithstanding, that this chapter is one of the most fascinating in a fascinating book

Gouty Arthritis and Gout

THOMAS E WEISS, M.D., F.A.C.P., ALBERT SEGALOFF, M.D., F.A.C.P., department of medicine, Ochsner Clinic, and associate professors of medicine, Tulane University School of Medicine, New Orleans. Springfield, Illinois: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp 221. 60s.

IT is easy to form a mental image of gout as a rather solid and immutable part of medical science—perhaps because much of what is known of its manifestations and treatment crystallised so long ago. And indeed the classical descriptions of the disease, accurate as well as colourful, can never be superseded. But the fresh breezes of progress have reshaped some of the picture and much new knowledge has accumulated about the biochemical abnormalities of the disease and about its treatment.

This monograph provides a good review of the clinical features, dips into the biochemistry, and gives guidance about treatment which in general is sound. The reader uncertain about the use of uricosuric drugs and the benefits they can offer, or in search of information about the comparative value of colchicine and its newer rivals—phenylbutazone, corticotrophin, and steroids—in acute attacks will find the answers here. The text could be tidied up by cutting out a certain amount of repetition, and probenecid appears more than once under the hybrid designation "probenemid". The reader is brought on occasion to a jarring halt by sentences of formidable complexity.

The importance of differentiating gout from the type of rheumatoid arthritis in which short, severe, and often monarticular attacks are separated by periods of normal health is rightly emphasised, but serological tests for rheumatoid arthritis, invaluable in making the distinction, are not mentioned. The 394 references cover the subject thoroughly, and if the reader is left at times to reconcile conflicting evidence for himself the authors do at any rate avoid unjustifiably categorical judgments.

A Catalogue of the Portraits and other Paintings, Drawings, and Sculpture in the Royal College of Surgeons of England

WILLIAM LEFANU. Edinburgh: E. & S. Livingstone. 1960. Pp 72. 30s.

THE impressive colonnaded building which dominates Lincoln's Inn Fields is world-famous as a research institute, a centre for postgraduate surgical training, and a museum. It is not generally recognised as the repository of a valuable and unusual art collection, and this may be because almost thirty years have elapsed since a guide to it—now long out of print—was last published. We congratulate Mr LeFanu on his new catalogue, which lists in full the 360 pictures or statues to be seen in the college, with a brief description of each, and illustrations of about half of them.

It is a variegated collection that he has had to enumerate. The portraits range from those of past presidents with names which will endure as long as surgery is practised, to those of mysterious and anonymous nonentities (the picture reputed to be that of Jenner, for instance, is almost certainly of someone else). There are even a few undoubted charlatans (Joshua Ward owed no allegiance to this or any other College, and requested burial in Westminster Abbey largely on the strength of having devised a successful purgative, and a cure for piles). The artists run from William Hogarth, who depicted the Master, in 1748, of the Company of Surgeons, to William Clift, the first Conservator, who depicted himself. The Sicilian Dwarf keeps company with a hippopotamus (the latter is Stubbs at his very best; but of the former, Clift, who had seen the body, said it was "from recollection, very little like").

It is to be hoped that Mr LeFanu's work, and Mr McNeill Love's generosity in sponsoring it, will be the means of introducing the College's art treasures to many who are unfamiliar with them. After all, no surgical qualification is required to appreciate what a bargain Percivall Pott obtained when Romney executed his portrait for twenty-eight guineas; or to realise what particular difficulties Turner faced when he tried to catch Daniel Lambert's likeness (his sitter is said to have weighed fifty-two stone).

World Review of Nutrition and Dietetics

Editor: G. H. BOURNE, department of anatomy, Emory University, Georgia, U.S.A.; assistant editor, EILEEN M. H. WILSON. London: Pitman Medical Publishing Co. 1960. Pp 272. 60s.

SINCE 1931 *Nutrition Abstracts and Reviews* has helped those wishing to bring themselves up to date with the science of nutrition. Appearing quarterly, it publishes 4 review articles each year, generally of a high standard, and abstracts of practically all the literature on nutrition published in the same time. Within the past twenty years, however, annual publications containing only review articles have become increasingly common and this Review belongs to that class. The first volume, just published, contains 10 articles (in English) written by authors from the United Kingdom, United States, France, Japan, and Guatemala. The intention that each author shall be an acknowledged authority in his subject and that his review shall bear the imprint of his experience and critical judgment is certainly borne out by this volume, and the articles have a personal touch which makes them easy to read. E. V. McCollum's History of Nutrition, for example, bears the stamp of his long experience in the subject. The article on basal metabolism in the Japanese population by S. Suzuki is largely built round his own work, and should be widely read, for the Japanese work on this subject is good. There are also reviews on androgens and protein metabolism, the biosynthesis of vitamin C, vitamin B_{12}, nutritional factors in anæmia, the use of isotopes, neoplasia, nutrition in utero, and (inevitably nowadays) kwashiorkor.

The book has a good index and is costly but well produced, without advertisements. The titles and legends for the figures are seldom sufficiently informative to be intelligible without referring to the text.

This new venture should have a wide appeal to students, teachers, and investigators, and if it can maintain its originality it should have a happy future—good luck to it!

The Handling of Chromosomes (3rd ed. London: George Allen & Unwin. 1960. Pp 248. 30s.)—This new edition of a well-known small handbook by Prof. C. D. Darlington and Mr L. F. La Cour on cytogenetic technique can be read with interest and profit by any of the numerous medicals who have been attracted to human chromosome studies by the spectacular recent advances. It is true that they will find little direct help, for species are treated here (and a very wide range is covered) solely as sources of material to demonstrate the variations in chromosome behaviour, and man receives only brief occasional mention. It is disappointing to find no discussion of tissue-culture methods. But the new advances in human cytogenetics are based on a very much larger range of work in other species, chiefly flowering plants and insects, and it is important not to neglect this background, if only to ensure realisation of the very wide range of techniques available in special circumstances. This is a remarkable little book, beginning with instructions on how to set up a microscope and ending with the writing of a paper, and it is full of information on a great variety of topics. It might be even more useful if it offered an example or two of detailed analysis of the appearances seen down the microscope, though the very beautiful plates afford some help in this respect.

Medical Directory 1960 (London: J. & A. Churchill. In two parts. £5.)—This year the two volumes of the directory contain 93,224 names, almost 2000 more than in 1959. Their price has also increased, but they are still well worth the money.

British Formulary 1960.—The price of interleaved copies is 11s. 6d., not 16s. 6d. as we stated last week.

THE LANCET

LONDON 28 MAY 1960

Griseofulvin

In August, 1958, Gentles[1] showed that guineapigs experimentally infected with *Microsporum canis* and *Trichophyton mentagrophytes* could be cured by griseofulvin At this time Blank and Roth[2] had under their care a unique case of widespread *T rubrum* granulomas which seemed likely to end fatally Stimulated by Gentles' paper they sought and were given griseofulvin This patient, the first to be treated by the drug, dramatically recovered The first published account of the clinical use of griseofulvin was that by Williams et al[3] in December, 1958 Since that time well over a hundred papers on the clinical aspects alone have been published all over the world The burden of their song has been very much the same Massed choirs met at international symposia in Miami last October and in London under the wing of the St John's Hospital Dermatological Society on May 13 and 14 to add their pæans of praise They sang, for doctors, in surprisingly close harmony The main theme has been the remarkable success of griseofulvin, with pitch according to skill and experience More recent variations have wandered a little into the more pensive, minor keys as certain problems and failures have become evident.

The most important use of griseofulvin is in the treatment of ringworm of the scalp cure, whichever the fungus concerned, is the rule Kirk and Ajello[4] reported in the U S A the first large successfully treated series In this country ringworm of the scalp is rare and our experience limited Meara[5] has reported the cure of 31 children, with no failures, although some required a second course of treatment More important is the unvarying success in the treatment of favus of the scalp At the London symposium Rivalier[6] reported the results of treating 180 children with ringworm of the scalp at the Saint Louis Hospital in Paris, 42 of these had favus treated without a single failure Favus is endemic in many Middle East countries, Pettit[7] has said that 10% of patients attending a skin clinic in Azerbaijan had favus, and at the symposium he reported that he had cured 75 out of 107 patients with favus, the failures being due largely to social reasons beyond his control[8] The possibility clearly exists of eradicating this infection, hitherto a therapeutic headache (That X-ray epilation with all its risks can now be discarded is a great relief) The rate of cure depends on the rate of outgrowth of infected hair, and infection will remain until this hair either breaks off or is mechanically removed It is generally agreed that the hair should be snipped off or shaved after three or four weeks of treatment by griseofulvin Daily local application of an antifungal preparation, combined with a shampoo, for a week or two after apparent cure will help to prevent reinfection Infected brushes and caps have still to be destroyed

The second indication for griseofulvin is in the treatment of fungus infections of nails On an earlier page Dr Russell and his colleagues describe their results, mainly in the treatment of *T rubrum* infections The findings closely parallel those of others, but this study is notable for its thoroughness Again with nail infections, the rate of cure depends on the outgrowth and the shedding of the infected tissues Fingernails take six months to be cured, at the recent symposium Williams[9] reported apparent failure in 3 of 50 cases Infected toenails, on the other hand, are less easily dealt with Diagnosis of the disease can be difficult—as difficult as the decision whether cure has taken place, for the rate of growth is so slow that cure can rarely be expected in less than a year Russell found cure in only 6 out of 19 patients treated for eleven months, and Peterkin[10] in 9 out of 37 This is the general experience The slow outgrowth of toenails must account at least partly for the many failures, the older the patient, the slower the growth Speeding the growth by avulsion of nails, combined with griseofulvin by mouth, leads to more certain and more rapid cure[11] Interest is now shifting to the problem of reinfection as more and more patients seem to be cured Will those people who catch ringworm of the nails repeatedly catch it every time they are "cured"? Reinfection has already been reported

Fungus infections of the skin generally respond extremely well to griseofulvin, which is called for in the treatment of favus, Tokelau ringworm, and most *T rubrum* infections The other dermatophyte infections have usually responded in time past to local—and more economical—treatment The blistery eruptions on the palms and soles are readily cured by means of griseofulvin in about a month The scaling, hyperkeratotic type of infection, usually associated with *T rubrum*, on the palms can usually be cured in six weeks, but the similar state on the soles is more of a problem, examples are being found of both complete failure to respond and of clinical and mycological relapse while griseofulvin is still being taken There is no evidence of the development of in-vivo resistance

Williams[12] suggested some time ago that the interdigital clefts of the feet might be the real testing-ground for griseofulvin, and at the London symposium he could claim cure for only 10 of 59 patients with trichophyton infections between the toes All these patients had infections in other sites, possibly the response would be better in cases with infection limited to the clefts Why should patients whose nails, palms, and soles get better continue to have clinical and mycological infection between the toes? To this question there is no clear answer Combination of oral with local griseofulvin has been tried and found wanting SCOTT [13] described at the symposium her interesting work with autoradiographic studies of chlorine-tagged griseofulvin, which suggest that by either route griseofulvin can penetrate the keratin of skin But its failure to control cleft infections does not seem to be a matter of absorption alone, perhaps some factor in the keratin of the resistant areas breaks down the drug Is the fact that these areas are those without hair-follicles significant? Does an excess of sweat play any part?

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[1] Gentles J C *Nature, Lond* 1958, 182 476

[2] Blank, H Roth, F J *A M A Arch Derm* 1959, 79 259

[3] Williams, D I , Marten, R H , Sarkany, I *Lancet* 1958, ii, 1212

[4] Kirk J , Ajello, L *A M A Arch Derm* 1959, 80 259

[5] Meara R H *Brit J Derm* 1960 72 169

[6] Degos R Rivalier E Lefort P *Trans St John's Hosp derm Soc* (in the press)

[7] Pettit J H S *Brit J Derm* 1960, 72, 159

[8] Pettit J H S *Trans St John's Hosp derm Soc* (in the press)

[9] Williams D I *ibid*

[10] Peterkin G A G *ibid*

[11] Newcomer, V D International Symposium on Griseofulvin Miami, October 1959 (in the press)

[12] Williams, D I , Marten R H Sarkany, I *Brit J Derm* 1959 71 434

Griseofulvin has usually been administered in a dose of 1 g daily There are theoretical grounds for believing that doses at longer intervals might suffice Toxic effects in animals have been produced only by vast doses given by injection Mice have tolerated a dose as high as 50 g per kg body-weight given orally KOLLER,[14] at the symposium, disposed conclusively of the idea that griseofulvin could be regarded as a growth-inhibiting substance and showed that no neoplastic or other pathological effects resulted from long-continued administration Clinically griseofulvin has so far proved to be singularly free of toxic effects The natural tendency of patients to ascribe any malaise to the drug they are taking, particularly if it is new, is shown well in the trials by RUSSELL and his colleagues, in their series, side-effects were just as common in the controls, given dummy tablets Rashes occur, sometimes probably owing to the drug Headaches certainly develop, but they disappear even although administration is continued Diarrhœa, thirst, lack of coordination, and an enhancing of the effects of alcohol are all possible, but uncommon, effects Finally, there is no evidence whatever that griseofulvin has any serious effect on the bone-marrow

Accidents at Sea

" How to ditch without a hitch " may be all very well as a reassuring slogan for those about to cross the ocean in an aircraft, but things do not always go quite according to plan, and even in the present century of technical achievement many lives have been lost at sea Apart from the great peace-time disasters such as the loss of the *Titanic*, and, quite recently, of the *Princess Victoria* near Larne and the new Danish ship off Greenland, thousands of men were lost at sea in the first and second world wars and the great majority of these died in the water The great problem is to get the lifecraft away with the people in it dry Cold, accentuated by immersion, is the great killer Thirst and starvation become important only in long voyages in small boats, and such voyages are likely to become increasingly rare

A great deal of work has been going on behind the scenes since the late war Committees appointed by the Admiralty and the Medical Research Council have been active in this country, and similar bodies have been at work in North America and other parts of the world [1-5] Lieut -Commander NICHOLL's book [6] gives a very good account of these developments to write it he obtained a great deal of inside information, and his account is historically accurate, readable, and up to date

Lifebelts have been improved almost beyond belief, and waterproofed protective suits have been tested experimentally for those who must take to the water The great advance, however, has been the introduction of the inflatable rubber lifecraft This has a roof which gives protection against both cold and heat,[3] and has already many records of good service to its credit These craft have become a standard fitting on British trawlers and should have become so for the amateur's yacht They are not yet compulsory on vessels engaged in the international trade Inflatable lifecraft, which as a rule hold ten or twenty persons, are now made commercially on both sides of the Atlantic The trouble at present is to launch them successfully, full of their intending passengers, from a ship with high sides, but no doubt this will be successfully overcome The conventional lifeboat has nothing very much to recommend it in this respect

The food to be provided in these craft, and particularly the amount of water, has been carefully studied, and it has been shown that about 500 ml of fresh water a day, supplemented by about 100 g of glucose, should suffice to keep a person alive and well for many days [7-9] This is enough even in the tropics if the initial seasickness can be overcome by the use of drugs [10 11] and precautions are taken to minimise loss of water by evaporation through the skin [3]

To drink, or not to drink, sea water has been a matter of debate and considerable experimentation, much of it personal Despite the exploit of Dr BOMBARD in crossing the Atlantic as he did in a rubber raft, and his claim that he survived for many days on sea water and fish juice, the British school have always set their face against the practice A nicely balanced amount of sea water added to the fresh-water ration may help in certain instances, but the survival records in lifeboats in which sea water was used in the late war are bad,[2] and the Netherlands and West German delegations have reported strongly against it to the Maritime Safety Committee of the International Maritime Consultative Organisation [12]

Little has yet been done to implement many of these new discoveries, but in the next few years the life-saving appliances on passenger ships are likely to be extensively improved following the International Conference on Safety of Life at Sea, which is now being held in London, and all the work which has been going on in the scientific background for the past fifteen years

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[13] Scott A *Trans St John s Hosp derm Soc* 1960 (in the press)

[14] Koller P C *ibid*

[1] Holt W J *Trans Instn nav Archit , Lond* 1955, 97 331

[2] McCance R A , Ungley, C C Crosfill J W L Widdowson, L M *Spec Rep Ser med Res Coun , Lond* 1956 no 291

[3] Hervey G R *Sci News* 1955 38 1

[4] Calloway D H *U S Forces med J* 1960 11 103

[5] Nesbitt, P H Pond A W Allen W H The Survival Book London, 1959

[6] Nicholl, G W R Survival at Sea Southampton 1960

[7] Gamble, J L *Harvey Lect* 1947 42 247

[8] Hervey, G R McCance, R A *Proc roy Soc* B 1952 139 527

[9] Hervey, G R McCance R A *Proc nutr Soc* 1951, 13, 11

[10] Glaser, E M , Hervey, G R *Lancet* 1952 i 490

[11] Glaser E M , McCance R A *ibid* 1959 i 853

[12] Proceedings of the Merchant Marine Council, United States Coast Guard April 1960

Piperazine as an Anthelminthic

INTEREST in helminthic infections has been revived in the past decade by advances in therapy Piperazine, which in the early part of this century was widely used for the treatment of gout, was introduced as an anthelminthic in France in 1949 [1 3] and is now accepted as the treatment of choice for threadworms and roundworms In treating threadworms WHITE and STANDEN [4] achieved a cure-rate of 97% with a week's course of piperazine, compared with 70% with gentian-violet. Piperazine has been found ineffective against the whipworm (*Trichocephalus dispar*) [2 3 5] and, more disappointingly, tapeworms [6] and hookworms [7], but NAGATY and KHALIL [8] have reported from Egypt 55% successes in infections with the intestinal fluke *Heterophyes heterophyes*, which sometimes causes diarrhœa

TALYZIN,[9] in Moscow, described a new method of treating ascariasis in which oxygen was introduced into the bowel by duodenal intubation MALAVIYA and SARASWAT [10] compared oxygen with piperazine therapy and concluded that piperazine was superior, but their criterion of success—percentage reduction of fæcal egg counts—was not wholly satisfactory These workers pointed out that, although the cost of oxygen used for each patient was less than that of a single large dose of piperazine, oxygen treatment was in fact expensive because it necessitated admission to hospital with much skilled attention and was attended by a fairly high incidence of unpleasant side-effects

Much of our understanding of the pharmacology of piperazine is due to the brilliant laboratory studies and field work of O D STANDEN and his colleagues Working with pig roundworms maintained in suitable media, STANDEN [11] showed that the action of piperazine was not cytotoxic but paralytic, and NORTON and DE BEER [12] subsequently established that it blocked acetylcholine transmission at the neuromuscular junction These findings are in keeping with the clinical observation that roundworms passed after administration of piperazine are intact,[5] whereas those passed after treatment with tetrachlorethylene and oil of chenopodium are partly digested The practical implication is that allergic disorders due to absorption of digestion products are unlikely to follow piperazine therapy With such therapy the early evacuation of roundworms, recorded by WHITE,[5] led GOODWIN and STANDEN to attempt a single-dose treatment in their trials in Africa,[13 14] in which the average cure-rate was 86% A successful single-dose treatment has obvious advantages in simplicity, cheapness, and freedom from the transient neurotoxic effects occasionally associated with seven-day courses [15] Purging is unnecessary with piperazine, but, if a single dose is given, a costive patient is likely to retain some worms which can recover from the narcotising effect of piperazine [11 13]

Unfortunately *Enterobius vermicularis* is not amenable to in-vitro study, but its response to piperazine is probably similar to that of ascarids, since both are nematodes, and it was therefore reasonable to attempt a single-dose treatment of enterobiasis BUMBALO et al [16] treated enterobiasis with single doses of piperazine citrate, but disappointingly the cure-rate was only 43% Dr WHITE and Dr SCOPES [17] have lately described in these columns a trial in which they administered single doses of a granular compound containing piperazine phosphate with standardised senna to hasten the expulsion of paralysed worms Given in this way, piperazine phosphate, in a dose of 3 g for children under 6 years of age and of 4 g for children over 6 years of age, cured 97% Astonishingly, their control preparation, containing no senna, gave a cure-rate of 92% This striking contrast with BUMBALO's experience is so far unexplained, for STANDEN's group found no significant difference in the absorption and excretion rates of various piperazine salts [18] or in their in-vitro activity against roundworms [11] Further work should be done to solve this problem and also to show whether the cure-rate of ascariasis can be increased by combination of piperazine with senna

Annotations

"SPIRITUAL HEALERS" IN THE WARDS

Dr Cotton Cornwall, in a letter we print today, quotes the Bishop of Lichfield, who, writing to *The Times*, remarks that "the admission of 'Spiritual Healers' to hospital wards raises matters of considerable concern " Assuredly it does

Nobody practising medicine can now doubt that the onset and course of many ailments is determined to a greater or less degree by influences not strictly physical, few of us can suppose that surgical and manipulative procedures, drugs, regimes, radiotherapy and physiotherapy, and the other constituents of our physical armamentarium comprise the whole of medical treatment We know well that the state of health of what may be called "the spirit" powerfully influences that of the body with which it is commingled and every practitioner must on occasion have wished to refer intractably ailing patients to their spiritual adviser

There is thus abundant need, in hospital wards as elsewhere, for effective healers—or even comforters—of the sick or wounded spirit, and it was presumably in the belief that they fulfilled some such function, or were on a par with ministers of religion, that certain hospital management committees have given permission for members of the National Federation of Spiritual Healers to enter the wards as representatives of that body If that is so these management committees have misunderstood the concept of "spiritual healing" held by the Federation

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1 Fayard C Ascaridiose et pipérazine Thèse, Paris Abstr *Sem Hôp Paris* 1949, 35 1778
2 Mouriquand G Roman E., Coisnard J *J Méd Lyon* 1951 32 189
3 Turpin R Cavier R Savaton-Pillet, J *Thérapie* 1952 7, 108
4 White R H R Standen O D *Brit med J* 1953 ii 755
5 White, R H R *Lancet*, 1954 ii 315
6 Goodwin L G Standen O D *Brit med J* 1958 i 133
7 Goodwin L G Standen O D *ibid* p 135
8 Nagaty H F Khalil H M *Lancet* April 30, 1960 p 978
9 Talyzin F F *ibid* 1954 ii 314
10 Malaviya B K, Saraswat K Proceedings of Symposium on Chemotherapy p 162 1958
11 Standen O D *Brit med J* 1955 ii 20
12 Norton S de Beer E J *Amer J trop Med Hyg* 1957 6 898
13 Goodwin L G, Standen O D *Brit med J* 1954, ii 1332
14 Goodwin L G, Standen O D *ibid* 1958 i 131
15 White R H R, Standen O D *ibid* 1953, ii 1272
16 Bumbalo T S Plummer, L J Warner, J R *Amer J trop Med Hyg* 1958 7, 212
17 White R H R, Scopes, J W *Lancet*, Jan 30 1960 p 256
18 Standen O D Goodwin L G, Rogers E W, Stephenson, D *Brit med J* 1955 ii, 437

If the Federation's own "Advice to Healers" and its president's "Guide to Spirit Healing" can be relied on, the "healers" in the wards will not be concerned with the spirit or spiritual health of any patient to whom they minister, but with the application of "healing power" of which they believe themselves to be repositories or vehicles. This power, though unidentified, is apparently physical and can "travel through blankets with ease", it is transmitted by touch and is credited with remarkable therapeutic effects. "In the case of a growth situated in the bowels, it has repeatedly been found that, after spirit healing has been invoked, there is a most unusual heavy rectal discharge, of such a character that it cannot be mistaken for an ordinary motion. Whenever this has occurred, an immediate betterment has followed, even with patients whom the doctors have only given a few days to live. The obvious inference is that by some unknown means the healing guides have been able to dissociate the growth and expel it from the body."

"Spiritual" or "spirit" healing—the phrases are used as if equivalent—seems to have close affinities with spiritualism. "No healer should ever go under trance control when attending a patient in hospital" but, clearly, might expect to do so in "his place of healing"—presumably a private treatment room where "the healer is the responsible person". The president of the Federation, Mr Harry Edwards, writes: "Although the author has many times received information (of a highly evidential character) to establish that both Pasteur and Lister are closely associated with this healing work, he never appeals to them as spirit guides for any particular healing, but opens himself to be used freely by any healing guide." There seems also to be a looser association with manipulative therapy. "The healer should not undertake manipulations by himself. The medical staffs will resent this and they may be justified in thinking the healer is doing harm unless they know what is taking place." Much of the "Advice to Healers" inculcates restraint, tact, and conciliatory behaviour in the wards—excellent things in themselves but given a rather different complexion when preceded by the words "In these early days we shall need to proceed carefully . . ."

The whole situation is, to put it mildly, very curious. The Federation is unquestionably a body of persons practising a therapy of their own, not recognised in orthodox medicine. They are not medical ancillaries nor are they spiritual advisers or ministers of religion, the Churches' Council of Healing does not recognise them, yet they are to be admitted to the wards of hospitals to administer "healing power" through manual contact to patients for whose care and treatment the medical staff is responsible. It is true that they are to receive permission and are advised not to make approaches to patients at large. "If other patients ask for healing, the normal permission must first be obtained." But they will seem to these "other patients" to have the sanction of the hospital for what they do, although it can hardly be supposed that their ministrations will have been prescribed or directed by the medical staff.

The unanimous advice of the Regional Hospitals' Consultants and Specialists Association that members of the Federation should have no special privileges, and that management committees who have already given their permission should reconsider their decision, seems in the circumstances remarkably restrained.

ABDOMINAL DECOMPRESSION IN LABOUR

A PROMISING method for reducing the pain and duration of the first stage of labour by abdominal decompression was described last year by Heyns.[1] Several obstetric units in this country have been developing apparatus to test this technique, but clear conclusions have been delayed by practical difficulties involved in bringing about the required drop in pressure inside the plastic suit enclosing the abdomen. The choice of a suitable source of suction and the exact design and supply of suits are important factors in the success of the method and comfort of the patient. All leaks of air into the suit must be prevented, and this leads to excessive sweating and discomfort from pressure of the suit on the legs. These and other technical difficulties have evidently been largely overcome by Dr Scott and Mr Loudon, whose report appears on p 1181 of this issue. These workers have introduced ingenious modifications: their successful design of a light, discardable, polyethylene suit which allows the legs to remain free, and costs only 2*s*. to replace, is especially notable.

Their results, though not yet advanced enough for detailed analysis, have been most favourable. The relief from pain is convincingly indicated by the reluctance of their patients to have the suit removed for pelvic examination—which, fortunately, is not often necessary. The frequent finding of full dilatation of the cervix within three hours of the time at which distress from contractions first began must surely be unusual in primigravidæ, and supports the suggestion by Scott and Loudon that abdominal decompression profoundly alters uterine action. Internal tocography during decompression showed uterine contractions of normal duration. Further investigation along these lines may throw valuable light on the nature of pain in labour in relation to changes in intra-amniotic pressure. It is perhaps slightly alarming to read that "the conventional fœtal stethoscope can be used . . . the whole procedure being completed *in a few minutes*". It would be unfortunate if inconvenience in listening to the fœtal heart sounds reduced too much the frequency of auscultation. The technique may take a specially important place in the management of labours in which the fœtus is at greater than normal risk, when repeated observations of the fœtal heart sounds are essential. In such cases a continuous monitoring device which could be used without interrupting the decompression would be invaluable.

Certainly this paper will stimulate renewed interest in abdominal decompression in the management of labour, and we hope that clear evidence will shortly be forthcoming concerning its effect on the pain and duration of the first stage.

A HOPEFUL PACKAGE

RECURRENT disputes about pay between the profession and the Government have for years clouded the atmosphere of the National Health Service and diminished the enthusiasm and efficiency of those who work in it. In proposing new arrangements for keeping medical and dental remuneration under review, the Royal Commission hoped to avert these damaging conflicts and to secure some assurance for doctors and dentists that "their standards of living will not be depressed by arbitrary Government action". The Government's prompt acceptance of the Commission's report, and the outcome of last week's special representative meeting of the British Medical Association, have raised further hopes that a period of tranquillity is at last beginning, that this Government and its successors will do more than their forerunners to win the confidence of the profession, and that the lingering rancour and the dissatisfaction, which nearly brought the B M A. to the point of advising doctors to withdraw from the service, will now abate

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[1] Heyns, O. S. *Med. Proc. S. Afr.* 1959, 5, 121; *J. Obstet. Gynæc. Brit. Emp.* 1959, 66, 220. See *Lancet*, 1959, ii, 91.

The Minister of Health told Parliament on April 11 that the Government was "prepared to accept the Commission's recommendations as a whole as they stand provided that the doctors and dentists respectively for their part are ready to accept them on the same basis" Though many people had doubts about just what was meant by "as a whole", and the description "a package deal" was sometimes given a disparaging ring, the council of the B M.A., the Conference of Local Medical Committees, which also met last week, and the Joint Consultants Committee were all three in favour of accepting the Minister's offer and his invitation to begin without delay detailed discussions by means of Joint working parties Nevertheless the agenda for the representative meeting of the B M A was full of misgivings—chiefly about the Commission's proposals for a review body to advise the Prime Minister on the remuneration of doctors and dentists and about the suggested differential payments for general practitioners Would the profession have "access" or "direct access" to the review body? Why should doctors have to use the Government as a sort of post-office through which to communicate with the review body? Was not a merit-award system wholly unsuitable for general practice? When it came to the vote, however, there were very few who felt strongly enough on these questions to turn away the Government's offer for, as the chairman of the council of the B M A, Dr Solomon Wand, declared, any firm amendment of the council's recommendations would nullify the Government's offer

So, though the meeting was long, its outcome was seldom in doubt the Government's offer was accepted, working parties will be in action soon on the Royal Commission's proposals, and there can be no regrets about loss of excitement if the future is, in Dr Wand's words, "a little less exciting but more dignified and more rewarding"

SEX RATIO OF STILLBIRTHS

STATISTICS of stillbirths are among the less spectacular of the data supplied by the Registrar-General In England and Wales the stillbirth-rate declined only slowly, and, in contrast with mortalities in infancy and childhood, it still stands at more than half the figure for 1928[1] Causes of stillbirth are not registered in England and Wales, but are usefully analysed in the annual reports of the Registrar-General for Scotland These reports have supplied data of real biological value with respect to anencephalus and have helped to establish the existence of social-class correlations, geographical variations, seasonal cycles, and long-term secular changes in the rate[2] Difficulties over the reliability of diagnosis of other stated causes of stillbirth and the relative smallness of the Scottish figures have hindered further exploitation of the data, and most studies based on official statistics have been concerned with stillbirths as a whole They include studies of variation according to social class, maternal age and parity,[1, 3-5] and, recently, sex ratio[6]

Allan[6] observed that the sex ratio (M/F) of stillbirths in England and Wales was virtually static from 1938 to 1951 at about 1 17, after which it decreased progressively to 1 08 in 1957 in fact the absolute female stillbirth-rate rose, while the male stillbirth-rate remained almost constant. The sex ratio of Scottish stillbirths also fell between 1938 and 1957, but in a more complex manner which did not correspond with the pattern for England and Wales Neither in Scotland, nor in Denmark, nor in the Netherlands was there a rise in the absolute rate for females comparable with that observed in England and Wales Allan also shows that the recent English rise in female stillbirths was accompanied by a rise in male deaths in the age-period between 30 minutes and 24 hours after birth

The overall pattern is a challenge to anyone who likes to seek biological explanations, and for the time being the picture is perplexing rather than illuminating We need to know more of the possible parts played by secular changes in the incidence of anencephalus with its 1 3 M/F ratio, of possible effects of changes in birth-weight and prematurity-rates on the sex ratios of stillbirth and early death, and of the effects of changing incidences, survival-rates, and ages at death in other malformations and diseases (such as hyaline-membrane disease) with asymmetrical sex ratios We join with Allan in regretting that official figures for England and Wales, because they do not include the causes of stillbirth, cannot help in this search

CONGENITAL CYSTIC LUNGS

CONGENITAL cystic disease of the lungs, first described in the 17th century,[7] is still confused with acquired cysts of granulomatous origin[8] Oswald and Parkinson[9] showed, in a series of 16 cases, that cystic disease of the lungs could arise in various pathological conditions, but they were unable to exclude a developmental origin in only 2 Moffat[10] has now studied 9 cases, all in patients under 18 months of age, and claims that minor degrees are probably often unrecognised He shows that three different types of congenital abnormalities may give rise to a "honeycomb" lung and that two of the types may be found together in each of the types, the malformation may be either extensive, involving both lungs or individual lobes, or confined to a small part of one lobe The first type involved the air-passages at different levels in 2 cases large cysts involved almost a whole lobe with smaller loculi round the periphery, in 2 cases cysts involved terminal air-passages in which the actual level could not be clearly defined, while in another 2 the lesions were intermediate and focal, consisting of a few small cysts lined by ciliated columnar epithelium and connected with larger and smaller air passages In the cases with involvement of the terminal air passages, pyogenic inflammation was present, leaving some of the cysts lined with granulation tissue In the second type the cystic dilatation involved the lymphatics, and

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[1] Morris, J N Heady J A *Lancet*, 1955 i 342
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[3] Heady J A, Daly C, Morris J N *Lancet*, 1955, i, 395
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[5] Heady J A Stevens, C F, Daly, C Morris, J N *ibid* p 499
[6] Allan T M *Brit J prev soc Med* 1960 14 35
[7] Koontz, A R *Bull Johns Hopk Hosp*, 1925, 37, 340
[8] Cunningham G J Parkinson T *Thorax*, 1950 5 43
[9] Oswald N Parkinson, T *Quart J Med* 1949, 18, 1
[10] Moffat, A D *J Path Bact* 1960, 79 34

Moffat's findings fully confirmed the excellent firs description of this type by Laurence [11] the appearances were those of a cystic hygroma with lobules of expanded lung intermingled with the dilated lymphatics The third type also involved the interlobular septa and visceral pleura, and Moffat suggests that these were pleural elements nipped off during branching of the fœtal lung buds superficially, these cysts had a thin lining resembling the pleura, but deeper the walls were densely fibrosed and the lining was often desquamated and multinucleated Only 1 of Moffat's cases showed associated congenital abnormalities (a cystic kidney), and none showed any evidence in other organs of reticulosis or xanthomatosis

Recognition that such lesions are congenital and that they may be found without any generalised condition may lead to a fresh appreciation of the association of honeycomb lung and xanthomatosis or lipoid reticulosis The development of cysts in the lung was followed radiologically and by biopsy in McNeill and Cameron's [12] case of Hand-Schuller-Christian disease, undoubtedly the cysts were acquired, and it was not claimed to be a honeycomb lung In series of honeycomb lungs,[8] [13] unless xanthomatosis affects tissues beyond the lung, a granulation-tissue wall to cysts may well be the result of repeated pyogenic infection, in which case small amounts of fat may be found in macrophages and giant cells, and even when the xanthomatosis is generalised the cystic lung may be coincidental and not necessarily consequential Especially in older children and adults, a focal collection of cysts may be acquired,[14] and the frequency of this type is increasing with modern treatment of tuberculosis [15]

The immediate practical importance of recognising these congenital cystic lungs is this in very young children who have repeated attacks of bronchopneumonia or even just frequent " colds ", this condition may be at the root of the trouble, which can be treated by removing the affected part

MYELOGRAPHY

PROTRUSION of a lumbar disc can usually be diagnosed readily enough, and since in most cases the patient recovers on conservative treatment the type of protrusion and its exact level is often of academic interest only In the difficult case, and sometimes as part of the preoperative study of a patient, myelography may be undertaken Some surgeons condemn this investigation as unnecessary and perhaps dangerous, while others regard it as an essential preliminary to surgical treatment The discomforts and hazards of myelography are well known Headache is a common sequel, although it rarely persists Infection is a greater hazard, producing a meningitis which may be fatal Arachnoiditis [16] and pulmonary emboli [17] have also been recorded

Lansche and Ford,[18] reviewing 866 myelograms, stress the importance of a lateral indentation of the column on the anteroposterior view produced by a lateral disc protrusion An hour-glass deformity usually indicates a midline protrusion Defects in the filling of the root sleeves or complete or incomplete blocking of the column may also be present The overall accuracy in this series was 76%—i e, in these 76% correlation between clinical and radiological findings was complete Major discrepancies were noticed in 17% and minor discrepancies in 6% Errors were almost evenly distributed between false-negative and false-positive results, and clearly a myelogram must be considered only as part of the evidence of a disc lesion and not be given too much weight in deciding whether to operate In this series the proportion of spinal neoplasms masquerading as disc lesions was 1%, but most of these tumours were not discovered by myelography Both false negatives and false positives can be produced by posturing the patient [19]

These discrepancies must raise some doubt as to whether the procedure is worth while in a condition where clinical diagnosis is on the whole satisfactory Lansche and Ford recommend it as a routine preoperative investigation Many surgeons, however, are prepared to make a routine wide exposure of the two lowest lumbar discs in all cases, since double lesions are not uncommon If this plan is followed the value of myelography is restricted to the diagnosis of the high lumbar disc protrusion and of recurrent protrusion

LIVERPOOL MASS-RADIOGRAPHY CAMPAIGN

IN 1959 a four-week mass-radiography campaign was held in Liverpool, and, as 454,286 people were brought before the X-ray cameras, it is abundantly clear that the operation was successful 1045 cases of active pulmonary tuberculosis (2 30 per 1000 X-rayed) and 1163 cases of malignant neoplasm (0 35 per 1000 X-rayed) were discovered In Liverpool residents the rate of active pulmonary tuberculosis was 2 41 per 1000 (males 3 09, females 1 86) As expected the prevalence was greatest in elderly men in men over the age of 60 years the prevalence was 5 55 per 1000 In women the highest prevalence was found in the 35–44-year age-group (2 61 per 1000), which suggests that the infection no longer involves the young above all other age-groups

Large mass-radiography drives have now been held in Glasgow, Edinburgh, Liverpool, and Exeter, and a remarkable feature of these enterprises has been the close similarity in the public response In Glasgow 76% of the adult population turned out, in Edinburgh 84 5%, in Liverpool 76 5%, and in Exeter 75% It appears, therefore, that, with enthusiastic endeavour and close cooperation between medical and civic authorities, about three-quarters of the adult population of a large city can be persuaded to take part in such a survey To achieve a response of this magnitude, it is essential to exploit modern publicity methods—press, radio, television, cinema, posters, prizes, slogans, and so on—but the organisers of these campaigns are unanimous that the most important single factor making for success was the enthusiastic and untiring efforts of many voluntary workers When so much is heard these days of apathy in public affairs it is reassuring to learn of this generous effort in a good cause We hope that as declining rates of tuberculous infection make large-scale mass radiography campaigns unprofitable, this reserve of civic goodwill can be mobilised to assist in eradicating the disease from those sections of the community where it is especially prevalent

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Special Articles

A METHOD OF ABDOMINAL DECOMPRESSION IN LABOUR

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The application of negative pressure to the abdomen during the uterine contractions of the first stage of labour was first used by Prof O S Heyns of Johannesburg (Heyns 1959) He conceived the idea that, if the abdominal wall were drawn forward by such means, the uterus could become spherical during a contraction instead of being deformed into an ovoid (fig 1) When spherical, the uterus is in its optimal contracting position His experiments showed that pain was considerably relieved and the first stage of labour shortened

To test this method, apparatus has been developed in Edinburgh which differs somewhat from that described by Heyns It is a reliable and effective means of applying extra-abdominal negative pressure It is, moreover, cheap, and can be readily assembled in most maternity hospitals

Apparatus

The three main components are the suction, the plastic suit, and the cage

Suction

To be efficient, the sucker used must be capable of withdrawing at least 50 litres of air per minute The steam pipe venturi suction equipment that is a standard wall fitting in most labour wards is usually adequate

The degree of negative pressure produced by the sucker is much less important than the amount of air removed Electric suckers supplied for medical use can reach relative low negative pressures but are seldom capable of moving more than 20–30 litres of air per minute Vacuum-cleaner pumps, on the other hand, suck large amounts of air (in excess of 100 l per min.), but become easily strained when the flow falls abruptly, as it does after partial evacuation of the air from the decompression apparatus They are probably unsuitable therefore for this type of work. To test the efficiency of suction apparatus a simple gasometer is used If the suction proves inadequate (less than 50 l per min) it must be augmented from another source

The suction point is connected to the decompression unit by wide-bore rubber pressure-tubing The latter is led into the unit and lies freely under the cage placed over the patient's abdomen A T-shaped junction is inserted into the tubing, proximal to its entry into the unit (we have used a standard endotracheal tube connection with a perforated rubber cap for this purpose, fig 2) The sucker, which is running continuously, cannot evacuate the air within the suit until the patient occludes the rubber-capped end with her thumb This she does at the start of each uterine contraction The whole process is thus patient-controlled The pressure within the suit is measured by a gauge connected to the unit by separate tubing

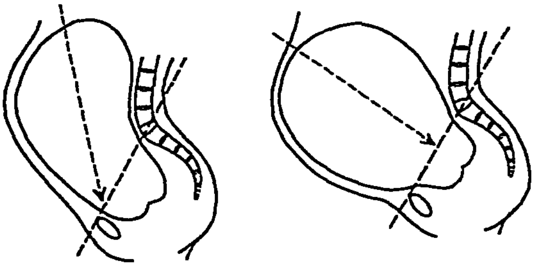
NORMAL
EXTRA ABDOMINAL NEGATIVE PRESSURE

Fig 1—Showing the theoretical change in the shape of the uterus during contractions under the influence of extra-abdominal negative pressure

Plastic Suit

Heyns advocates the use of a strong polyvinyl chloride suit enclosing the mother from feet to axillæ and fitted with a long airtight 'Zip'-fastener to allow access to the patient We have preferred a much thinner polyethylene ('Polythene') suit which allows free movement of the legs Thin polyethylene has the additional advantage that during evacuation of the air it becomes so tightly apposed to the skin that it tends to be self-sealing, whereas with thicker material, it is difficult to get an airtight fit Our suits cost about 2*s* and are discarded after use

Fig 2—The patient s thumb control

At first we enclosed the patients from feet to axillæ, but many complained of their inability to move their legs, which were pressed tightly together by the suit during the decompression Moreover, the total enclosure in polyethylene caused the feet to perspire unpleasantly To avoid this, a bag was devised to allow the legs to be outside (fig 3)

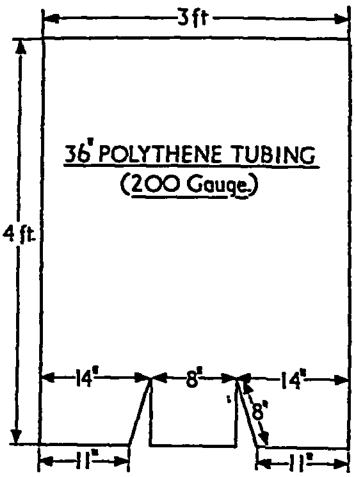

Fig 3—Diagrammatic representation of the dimensions and shape of the 'Polythene' suit

This is made from 200-gauge polyethylene tubing of 72 in circumference (i e, 36 in across when laid flat) A piece of this tubing 54 in long is cut into the shape shown in fig 3 by removing two small triangular pieces from one end The cut edges of these triangles are sealed by means of a small electric polyethylene welder, and reinforced with 'Sellotape' Thus, two leg holes are provided, and a central access port through which the suction tubing passes and rectal examinations can be made

Cage

The purpose of the cage is to maintain an air-space between the suit and the abdomen Without it the polyethylene would merely collapse on to the patient's skin and the abdominal wall would not move

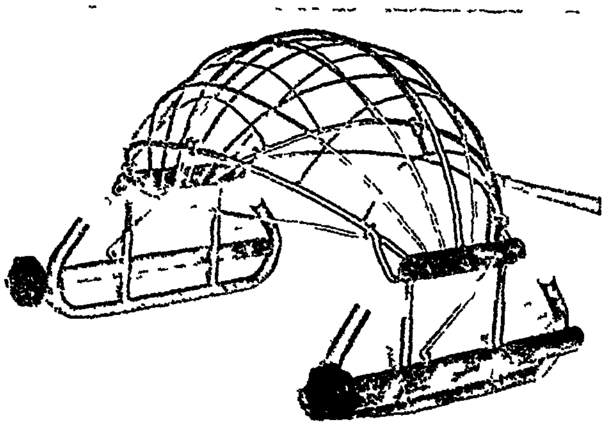

Fig 4—The adjustable cage

We have constructed our cages from steel rods so that they are strong and the abdomen can easily be viewed through the suit The cage should be fixed at a height anterior to the abdomen that will allow about 4–6 in of movement of the lower abdominal wall It should not encroach on the thorax, its upper edge being ideally situated 1 in anterior to the costal margin This eliminates any interference with respiration

During the application of negative pressure within the unit, a downward thrust of 100–200 lb is exerted by the atmosphere (50 mm Hg is equivalent to 1 lb per sq inch) Hence the cage must not rest on the patient at any point A simple way of ensuring this is to suspend it from a larger outer cage, which rests on the patient's bed The small cage is held, through the polyethylene, by retort clamps fixed to the outside cage Alternatively, a cage fitted with supports, which rest on the bed at each side of the patient, can be used alone, and this facilitates access to the patient By making these side supports adjustable, the great majority of women can be accommodated, and changes of position are easier

Our latest cage is shown in fig 4 This allows a wide range of movement, is quickly and easily adjusted, and is stable in all positions

Method

In placing a patient in the suit, the procedure is as follows

The legs are put through the leg holes and the polyethylene folded neatly round each thigh and secured with bandages A towel is placed under the patient's back, and the suit pulled up to the axillæ so that the towel lies between the skin and the polyethylene The cage, after being adjusted to a suitable height, is placed over the abdomen within the suit The suction tubing and the pressure-gauge tube, having been previously fastened to the underside of the cage, are passed through the central access port, and the polyethylene is secured round them by a bandage. The upper end of the suit is now drawn across the upper thorax and the excess folded under the patient's back This is secured by a bandage or wide rubber belt passed right round the thorax just below the axillæ Careful attention to making the suit airtight is essential Connection is then made to the suction apparatus and the pressure-gauge The suit is now ready for use (fig 5)

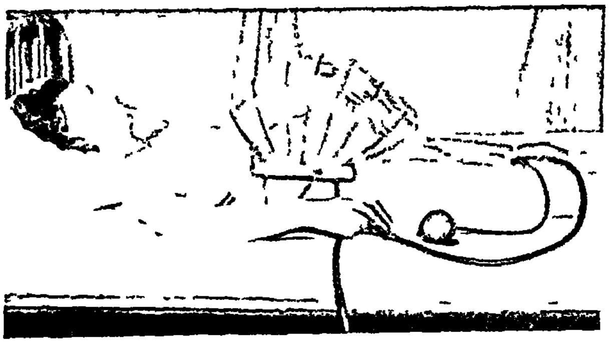

Fig 5—The apparatus ready for use

The patient is shown how to operate the simple valve with her thumb On evacuating the air from the suit, the abdomen is seen to rise forward a considerable distance (fig 6) The main movement occurs before the pressure has been lowered to −20 mm Hg, and the patient can keep the pressure between −20 and −40 mm Hg by allowing a small leak These pressures differ from those recorded by Heyns—probably because he measured the pressure by leading off a side tube from his suction line, and thus recorded the pressure in the line, which is considerably below that in the suit

The patient is told to apply the negative pressure only for the duration of a " pain "

To record the fœtal heart-rate, an electronic monitor such as that described by Simpson (1959) is ideal The conventional fœtal stethoscope can be used, however, simply by undoing the top seal, retracting the polyethylene, and tilting the cage so that the abdominal wall becomes accessible After auscultation of the fœtal heart, the cage and suit are replaced as before, the whole procedure being completed in a few minutes

For rectal examinations, the bandage securing the polyethylene round the suction tubing is released and the hand inserted into the access port

Though we have managed most of our patients in the supine position, it is quite easy to have them sitting in a chair (fig 7)

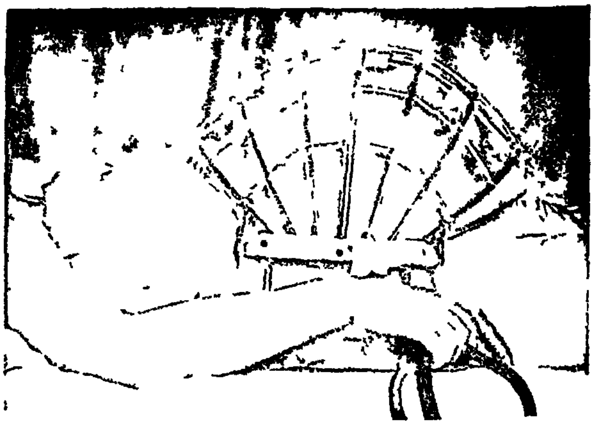

Fig 6a

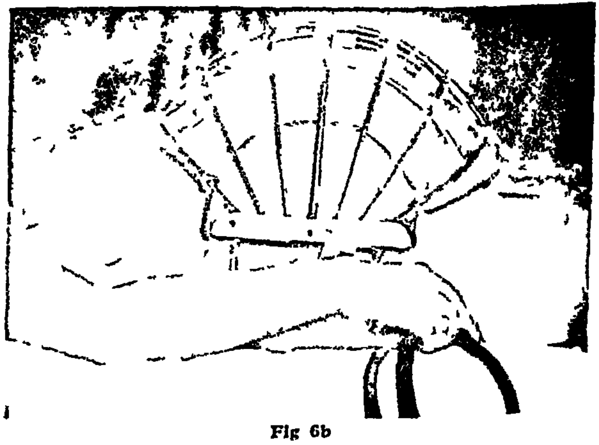

Fig 6b

Fig 6—(a) Before application of negative pressure
(b) During application of negative pressure showing considerable forward movement of the abdominal wall

Management

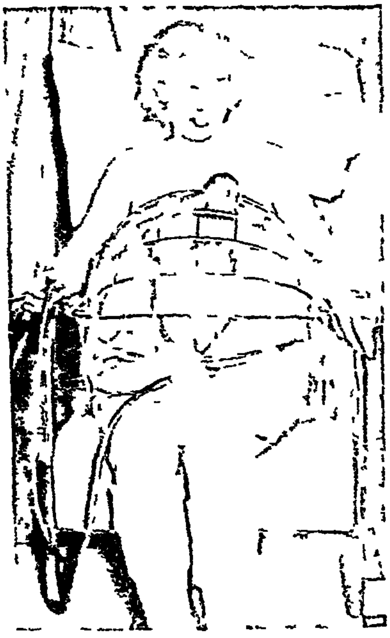

Fig. 7—The apparatus in use in the sitting position.

A patient is considered ready for decompression when she is just beginning to be distressed by the pain of her uterine contractions, and would normally be given some form of sedation. At this time the cervix is usually from one to three fingers dilated. To obtain uniformity between cases, and also because intact membranes delay the progress of labour (Bainbridge et al. 1958), we have ruptured intact membranes before commencing decompression.

After a brief demonstration of the apparatus, all our patients have been able to master the technique within a few minutes. The reduction in pain which immediately follows decompression is often so complete that the patient cannot tell when a uterine contraction has ceased, and she tends to maintain negative pressure for much longer than the average length of uterine contractions at this stage in labour. This led us to think that the contractions were prolonged, but internal tocography has shown that they are not.

As labour progresses, pain may reappear, although still considerably less than when negative pressure is not applied. We have not withheld analgesics if the patient feels discomfort, pethidine (100 mg.) being the drug we have preferred. Usually this is not needed until the cervix is almost fully dilated, and often it is not needed at all.

With increasing experience, little difficulty has been found in judging the progress of labour. Rectal examination is possible through the central access port. To allow an aseptic vaginal examination the suit must be removed—an unpopular move if the patient is obtaining relief. We now find, however, that pelvic examination is seldom required. Pain reappearing after two or three hours' decompression usually indicates that the cervix is nearly fully dilated. There is a temptation to carry out a vaginal examination at this time, but we now prefer to await the onset of convincing expulsive contractions (giving pethidine if necessary), because premature removal from the suit may delay the final stage of cervical dilatation.

Not every case will achieve this ideal course of labour. Backache associated with contractions is usually well relieved by this technique, but occasionally severe backache, persisting between contractions, has necessitated removal of the patients from the suit because they can no longer tolerate lying supine. Most of our patients have been managed in this position, but we are now finding that the sitting position removes this troublesome complication. Occasionally a patient loses morale and cannot cooperate fully.

To decide how far the first stage of labour is shortened, as demonstrated by Heyns, is difficult because one cannot fairly compare the time from commencement of decompression to full dilatation with the total length of the first stage in cases untreated by this method. In an attempt to obtain more exact information, we have used the method almost exclusively for primigravidæ, in whom the cervix is one to three fingers dilated and whose membranes have been ruptured. As a control series similar cases without decompression are being followed. These trials cannot yet be assessed, but the fact that a very high proportion of cases who receive decompression reach full dilatation in under three hours appears to substantiate Heyns' claims.

We are satisfied that abdominal decompression is harmless to mother and fœtus and profoundly alters uterine action. It therefore deserves further investigation and wider application.

To Prof. R. J. Kellar, who first described this method to us after a visit to Professor Heyns in Johannesburg, we wish to record our gratitude for his constant encouragement during this work. We should also like to thank those obstetricians of the Simpson Maternity Pavilion who have allowed us access to patients under their care, and also Dr. D. C. Simpson of the medical physics department of the University of Edinburgh.

The cages used in these experiments were made by Buccleuch Radio and Light Engineering, Edinburgh.

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GENERAL MEDICAL COUNCIL

In his address at the opening of the Council's 200th session on May 24, Sir DAVID CAMPBELL, the president, said that the committee appointed in 1958 by the United Kingdom Atomic Energy Authority to examine generally the provision of training in problems of radiological health and safety for all persons had recommended that medical schools should consider including in the basic medical curriculum some instruction in the use and hazards of ionising radiations. Such instruction need not be elaborate, but should give a clear picture of the scientific principles involved and the significance of the effects. This recommendation was in no way incompatible with the Recommendations as to the Medical Curriculum adopted by the Council in 1957, which left the provision of instruction in the more specialised fields of medicine and surgery to the discretion of the medical schools. It rested accordingly with the authorities of each licensing body and medical school to consider this matter in the light of that recommendation.

A little over two years ago the *British Pharmacopœia, 1958*, was published. At its meeting that morning the Pharmacopœia Committee approved on behalf of the Council an *Addendum*, prepared by the Pharmacopœia Commission. The *Addendum* would be published on Oct. 3, and would become effective on March 1, 1961.

In January the Council and the Pharmacopœia Commission independently had received letters from the Ministry of Health stating that the Minister, in consultation with the Home Secretary and the Secretary of State for Scotland, had set up an Interdepartmental Working Party "to review the legislative provisions which relate to the control of medicinal substances and to recommend what changes should be made to rationalise and simplify the law with a view to ultimate amendment and consolidation." In the opinion of the Pharmacopœia Commission the issues raised went much deeper than the tidying up of a somewhat ill-fitting mosaic of statutes. It seemed desirable to examine afresh, in the light of recent advances, fundamental questions concerning not only the inclusion of drugs in the *Pharmacopœia* but also the frequency with which specifications of such drugs (which had the full authority of the *British Pharmacopœia*) should be issued by the Council on the advice of the Pharmacopœia Commission There was a further question, even more difficult, which could hardly be ignored altogether—namely, the question of the best way of protecting the public in regard to new drugs, not always without danger to the public Possibly some scheme, involving legislation, needed to be evolved for the evaluation of new drugs before they were sold to the public

In conclusion the President referred to the report of the Departmental Committee on Powers of Subpœna of Disciplinary Tribunals, which is summarised in this issue on p 1186

HEALTH SERVICE IN SCOTLAND

EXPENDITURE on the hospital building programme in Scotland is expected to be of the order of £3,300,000 in 1960–61 and £3,900,000 in 1961–62 These figures are recorded in the report for 1959 of the Department of Health for Scotland,[1] which states that authority has been given for preliminary planning of the first phases of four complete new teaching hospitals in Glasgow, Edinburgh, and Dundee, and for major extensions to teaching hospitals in Glasgow and Aberdeen It seems fairly clear, says the report, that the hospital service can look forward to the substantial replacement of many outworn or outmoded hospitals

Under the general oversight of the Department's Hospital Planning Committee, a hospital development unit, composed of architects, doctors, a surveyor, and other professional officers, has been set up The unit, working closely with the Scottish Hospitals Work Study Group, is mainly concerned with formulating advice on planning and methods of construction, and at the end of the year it was studying hospital casualty departments and the space requirements of the various elements comprising a ward unit

Between June, 1958, and September, 1959, almost 1000 tuberculosis beds became redundant In round numbers, of 775 that were reallocated, 420 were allotted to the chronic sick, 100 to general medicine, 140 to surgery, 50 to infectious diseases other than tuberculosis, 30 to convalescent patients, and 35 to miscellaneous purposes The majority of the remaining redundant beds are closed temporarily

At the end of the year there were 63,860 staffed beds in the service—a decrease of 90 on the figure at the end of 1958 During the year 558,000 patients were discharged and 2,337,000 new outpatients treated, the 1958 figures were 537,000 and 2,558,000 respectively The average weekly cost per patient in the year ended March 31, 1959, was £13 8*s* 6*d*, compared with £12 17*s* 2*d* the previous year, the average cost of outpatient treatment was 11*s* 1*d* per attendance, compared with 10*s* 9*d* the previous year

During the year holiday exchanges of patients took place between a mental hospital in Ayrshire and one in Edinburgh, and between the Ayrshire hospital and an English hospital The patients selected for this exchange would otherwise probably never have had an opportunity of a holiday or a change of scene Some nurses from the parent hospital accompanied each group of patients "The results of the holiday, measured in terms both of therapeutic value and of enjoyment by the patients (and of pleasure to their relatives), have been most encouraging"

The Scottish Medical Practices Committee granted during the year 7 applications to set up new singlehanded practices Such applications, says the report, are few chiefly because of the difficulty, even with an initial practice allowance, of building up from scratch an adequate list of patients

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[1] Report of the Department of Health for Scotland 1959 H M Stationery Office Pp 133 7*s*

Points of View

THE CAUSE OF ŒDEMA IN "COR PULMONALE"

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HEART-FAILURE is hard to define, but in patients with cardiovascular disease the combination of ankle and/or sacral œdema and engorged neck veins is generally regarded as indicating impaired cardiac function, the œdema being attributed either to back-pressure or to a reduction in cardiac output which causes sodium retention by diminishing renal blood-flow or in some other way

A number of factors are thought to contribute to heart-failure in chronic lung disease—e g, reduction in the pulmonary vascular bed (which may be partly irreversible), hypoxia, polycythæmia (and hypervolæmia), and chest infection These factors cause pulmonary arterial hypertension, and may ultimately lead to myocardial failure

We feel that this explanation does not adequately account for œdema in chronic lung disease We shall review the evidence that has caused our dissatisfaction, and propose a fresh interpretation

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The circulatory dynamics in cor pulmonale differ from those in most other varieties of heart-disease In patients with heart-failure due to rheumatic or degenerative forms of heart-disease the cardiac output is reduced, but in patients with heart-failure due to emphysema it is generally agreed (Ferrer and Harvey 1959) that output is often normal, and may even be higher than normal With recovery from failure, the output rises or remains unchanged in patients with degenerative forms of heart-disease, whereas in emphysema it usually falls

In chronic lung disease œdema is not closely correlated with right ventricular hypertrophy, raised venous pressure, or pulmonary hypertension Fulton (1953) in a study of cor pulmonale found that 4 patients in whom he had made this diagnosis during life had no right ventricular hypertrophy at necropsy He also noted that, in a group of cases characterised by severe anoxia, œdema was present although the heart was radiologically normal or very little enlarged The electrocardiogram (E C G) showed no definite evidence of right ventricular hypertrophy, and even at necropsy the hypertrophy was usually only slight These observations are difficult to reconcile with the view that œdema is simply due to right heart-failure resulting from pulmonary hypertension Moreover, Mounsey et al (1952) have shown that in cases with venous congestion and œdema the right ventricular systolic pressure may be only slightly raised Of 8 patients catheterised in "congestive failure", 4 had systolic pressures between 36 and 47 mm Hg (normal 13 to 30 mm Hg)

On several occasions we have observed pitting œdema of the legs, of recent onset, in the presence of a normal jugular venous pressure This is all the more significant because in chronic lung disease the jugular venous pressure may be slightly raised without necessarily indicating heart-failure (Wood 1956) Simpson (1959) has observed that the so-called heart-failure in the emphysematous patient who is anoxic and hypercapnic but not suffering from an acute chest infection sometimes fails to respond to the usual diuretic measures but may disappear spontaneously

We do not wish to suggest that the sequence

pulmonary hypertension→right ventricular hypertrophy→
right ventricular failure→venous engorgement→œdema

never occurs in lung disease But it may not be the invariable sequence in patients who become œdematous, and it may in fact be uncommon

In chronic lung disease the correlation between œdema and polycythæmia or infection is as poor as that between œdema and pulmonary hypertension Many patients with œdema have normal hæmoglobin and red-cell concentrations On the other hand, one occasionally sees patients with considerable polycythæmia (hæmoglobin concentration over 20 g per 100 ml) without œdema Shaw and Simpson (1959) found no significant difference in the red-cell mass of patients with and without œdema who had lung disease and anoxia of comparable severity Similarly, infection can be present without œdema and œdema without infection

RESPIRATORY FUNCTION AND ŒDEMA

Œdema and venous congestion occur in a variety of conditions which adversely affect respiratory function In some, such as chronic bronchitis and emphysema, there is considerable destruction of the lungs and pulmonary vascular bed, in others, such as kyphoscoliosis or failure of the respiratory centre, the lungs are comparatively normal The only functional abnormality that is constantly present is a reduced alveolar ventilation as shown by an elevated arterial CO_2 tension This, of necessity, is always associated with a reduced arterial O_2 tension, and the relative importance of the elevated CO_2 tension and reduced O_2 is difficult to evaluate

From the data of the last decade the following generalisations are possible

Œdema is rarely present if the pCO_2 is normal
If œdema is present the pCO_2 is almost always raised
The pCO_2 may be raised without œdema being present

Anoxæmia is usually more severe in patients with œdema, but there is considerable overlap In conditions where anoxia occurs without CO_2 retention (e g, diffuse interstitial fibrosis) œdema has not been reported

These generalisations are based on personal observations and an examination of the literature since blood-gas measurements came into use The most important papers are with reference to emphysema, Donald et al (1952), Platts and Greaves (1957), with reference to kyphoscoliosis, Hanley et al (1958), Bergofsky et al (1959), with reference to the hypoventilation syndrome, Auchincloss et al (1955), Burwell et al (1956), Carroll (1956), Richter et al (1957)

The literature is not always easy to interpret, (1) because cor pulmonale is defined in different ways and œdema is not always mentioned, and (2) because in some series (e g, Bergofsky et al 1959) some of the blood-gas studies were performed after recovery from "congestive failure" when the pCO_2 may return to normal From published reports, from the experience of Bradley (1959), and from personal observation, only 2 out of more than 150 patients have been found who had a normal pCO_2 at the time œdema was present One of these was patient no 1 of Platts and Greaves (1957) who had pulmonary fibrosis and pulmonary artery thrombosis One other patient (A P of Donald et al) probably had œdema with a normal pCO_2 Simpson (1959) has records of 98 patients with chronic lung disease who had œdema at some time 16 had a normal pCO_2, but most of these, in addition to lung disease, had other conditions causing œdema 9 had hypertension, 1 had atrial fibrillation, and 1 ischæmic heart-disease Of the remainder, 1 had slight and very transient œdema, leaving only 4 who had œdema, normal pCO_2, and no cause other than lung disease

It would obviously be desirable to know whether the elevated pCO_2 or the reduced oxygenation of the blood is the more important disturbance, and also to discover the physiological mechanism by which it causes fluid retention In all conditions causing "cor pulmonale" anoxæmia can be relieved by breathing oxygen, but the pCO_2 can be lowered only by increasing alveolar ventilation This increase can be achieved by stimulating the breathing, by assisted ventilation, or by using drugs which reduce the mechanical resistance of the lungs and airways These facts mean that the relative importance of the respiratory acidosis and the anoxæmia should be ascertainable by a controlled experiment in which one group of patients was treated with oxygen and another by increased ventilation Such an experiment would, however, be unethical, because both the respiratory acidosis and the anoxæmia are almost certainly harmful and should be treated Furthermore, besides reducing respiratory acidosis, an increase in ventilation would relieve anoxæmia (unless the inspired air was made deficient in oxygen, which again would be clearly unethical)

There is, however, one recent observation which suggests that the respiratory acidosis is more important than anoxia Kellaway (1959) noted that œdema tended to increase during the first few days when patients with severe chest disease, CO_2 retention (as judged by increased CO_2 combining-power), and anoxia were treated with continuous oxygen This evidence is difficult to confirm, because, unlike those in Kellaway's series, such patients usually receive diuretics

SUGGESTED MECHANISM OF FLUID RETENTION AND ŒDEMA FORMATION

The coincidence of respiratory acidosis and œdema does not of course prove a causal relationship But we are justified in considering such a possibility

Increase of blood pCO_2 increases the formation of carbonic acid in the renal tubular cells The hydrogen ions are excreted into the tubules in exchange for sodium ions which are passed together with the bicarbonate ions into the blood This increased reabsorption of "bicarbonate-bound base" has been shown in dogs to be greater in chronic respiratory acidosis (Sullivan and Dorman 1955) This mechanism, therefore, could lead to an expansion of the extracellular fluid and would be expected to meet opposition from the "volume" regulating mechanism Presumably the balance of this antagonism would determine whether or not œdema develops Studies of aldosterone secretion may support or disprove this hypothesis Even should it be disproved, the acidosis could operate at other sites controlling body-fluid regulation, without necessarily involving the heart

A factor which might be important in potentiating the mechanism suggested above has been noted by Chernıack (1956) and Hammond (1957) They found that, in patients with emphysema, when œdema is present, the seemed desirable to examine afresh, in the light of recent advances, fundamental questions concerning not only the inclusion of drugs in the *Pharmacopœia* but also the frequency with which specifications of such drugs (which had the full authority of the *British Pharmacopœia*) should be issued by the Council on the advice of the Pharmacopœia Commission There was a further question, even more difficult, which could hardly be ignored altogether—namely, the question of the best way of protecting the public in regard to new drugs, not always without danger to the public Possibly some scheme, involving legislation, needed to be evolved for the evaluation of new drugs before they were sold to the public

In conclusion the President referred to the report of the Departmental Committee on Powers of Subpœna of Disciplinary Tribunals, which is summarised in this issue on p 1186

HEALTH SERVICE IN SCOTLAND

EXPENDITURE on the hospital building programme in Scotland is expected to be of the order of £3,300,000 in 1960–61 and £3,900,000 in 1961–62 These figures are recorded in the report for 1959 of the Department of Health for Scotland,[1] which states that authority has been given for preliminary planning of the first phases of four complete new teaching hospitals in Glasgow, Edinburgh, and Dundee, and for major extensions to teaching hospitals in Glasgow and Aberdeen It seems fairly clear, says the report, that the hospital service can look forward to the substantial replacement of many outworn or outmoded hospitals

Under the general oversight of the Department's Hospital Planning Committee, a hospital development unit, composed of architects, doctors, a surveyor, and other professional officers, has been set up The unit, working closely with the Scottish Hospitals Work Study Group, is mainly concerned with formulating advice on planning and methods of construction, and at the end of the year it was studying hospital casualty departments and the space requirements of the various elements comprising a ward unit

Between June, 1958, and September, 1959, almost 1000 tuberculosis beds became redundant In round numbers, of 775 that were reallocated, 420 were allotted to the chronic sick, 100 to general medicine, 140 to surgery, 50 to infectious diseases other than tuberculosis, 30 to convalescent patients, and 35 to miscellaneous purposes The majority of the remaining redundant beds are closed temporarily

At the end of the year there were 63,860 staffed beds in the service—a decrease of 90 on the figure at the end of 1958 During the year 558,000 patients were discharged and 2,337,000 new outpatients treated, the 1958 figures were 537,000 and 2,558,000 respectively The average weekly cost per patient in the year ended March 31, 1959, was £13 8*s* 6*d*, compared with £12 17*s* 2*d* the previous year, the average cost of outpatient treatment was 11*s* 1*d* per attendance, compared with 10*s* 9*d* the previous year

During the year holiday exchanges of patients took place between a *mental hospital in* Ayrshire and one in Edinburgh, and between the Ayrshire hospital and an English hospital The patients selected for this exchange would otherwise probably never have had an opportunity of a holiday or a change of scene Some nurses from the parent hospital accompanied each group of patients "The results of the holiday, measured in terms both of therapeutic value and of enjoyment by the patients (and of pleasure to their relatives), have been most encouraging"

The Scottish Medical Practices Committee granted during the year 7 applications to set up new singlehanded practices Such applications, says the report, are few chiefly because of the difficulty, even with an initial practice allowance, of building up from scratch an adequate list of patients

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[1] Report of the Department of Health for Scotland 1959 H M Stationery Office Pp 133 7*s*

Points of View

THE CAUSE OF ŒDEMA IN "COR PULMONALE"

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On several occasions we have observed pitting œdema of the legs, of recent onset, in the presence of a normal jugular venous pressure This is all the more significant because in chronic lung disease the jugular venous would in our opinion be intolerable if the course of justice was defeated by the withholding of evidence in such cases "

Disciplinary tribunals, the committee concludes, perform a valuable function for the benefit of the public, and it is the duty of all authorities and persons whether in uniform or not, to assist them to the best of their ability

A.I D. not necessarily Approbation of Marriage

In 1944 a ceremony of marriage was contracted between parties of which the husband was impotent as the result of an accident. There was, at that time no possibility of improvement in his condition and that remained the position at all material times In June, 1950, the wife gave birth to a child as the result of A I D to which the husband had consented The child was registered in the name of both parties The wife filed a petition seeking a decree of nullity on the ground of the husband's incapacity to consummate the marriage The suit was undefended.

Mr Commissioner LATEY, Q C., remarking that the legality of the form of registration of the child was not a matter upon which he was prepared to express an opinion in view of the uncertain state of the law on more than one aspect of A I D, said that the birth of the child in 1950 gave rise to the question whether the wife had, thereby, approbated the marriage

The law as to approbation in nullity suits when both parties had consented to artificial insemination was summarised in paragraph 286 of the report of the Royal Commission on Marriage and Divorce. The conduct of the wife in permitting artificial insemination followed by the conception of a child did not necessarily amount to approbation if there was no intention on her part to acquiesce in the marriage should the husband remain impotent after the birth of the child The test was whether the conduct and overt acts of the wife were consistent only with an affirmation of the existence and validity of the particular marriage, whatever might be its particular attributes Conduct which might amount to approbation would not be so regarded if, at the material time, the petitioner was unaware that, on the facts and the law, the marriage could be annulled

The Royal Commission recommended that where the parties had gone to the length of artificial insemination of the wife, whether by the husband or a donor, that should constitute such a fundamental step that it amounted to an acquiesence in the marriage and it was undesirable that either of them should, thereafter be allowed to claim that the marriage should be annulled on the ground of the impotence of the other That recommendation had not, however, been adopted by the legislature and the present case fell to be decided by the existing law

It was clear, on the evidence, that at the time the wife went through the process of A.I D she had no knowledge of the legal remedy open to her in view of the husband's incapacity Her act in so doing did not, therefore, amount to approbation of the marriage and she was entitled to a decree *nisi* of nullity

Q orse T v Q—*Probate Divorce and Admiralty Division* Mr Commissioner Latey Q C. May 11 1960 Counsel and solicitors R B Holroyd Pearce and N A Medawar (Wildman, Willington & Wallace

ELAINE JONES
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The D.A O and "Reasonable Care"

A woman who had become deeply upset over her son s proposed marriage was under the care of her doctor, who decided that she required observation and psychiatric treatment which she could not get at home, and he asked the duly authorised officer to the local health authority to call on her When the officer called, the domestic troubles had reached a crisis and he found her in a distressed condition Later the doctor arrived. The woman was asked to sign an application for admission to a mental hospital as a voluntary patient but refused to do so With the doctor's agreement the officer summoned an ambulance and had her removed to a mental institution, purporting to act under section 20 of the Lunacy Act 1890 She was discharged after four days, the magistrate refusing to make a reception order

The woman and her husband thereupon sought, and obtained, the leave of the High Court to bring proceedings against the officer, having satisfied the Judge on affidavit evidence, as required under the relevant provisions of the Lunacy Act 1890, as amended by the Mental Treatment Act 1930, that there was " substantial ground for the contention " that the officer had acted " without reasonable care " There was a conflict on the affidavit evidence filed for the proposed plaintiffs and for the officer The officer stated that he had formed the impression that the woman had become emotionally unstable and unbalanced, the doctor going no further than to say that she was suffering from a serious and prolonged emotional disturbance and required observation and psychiatric treatment and skilled attention which she could not get if she remained at home

The officer appealed against the grant of leave to bring proceedings against him. The Court of Appeal dismissed his appeal

Lord Justice ORMEROD said that section 20 of the Act of 1890 under which the officer had purported to act in removing the woman to hospital brought into operation section 14 of the same Act, which required *inter alia* that before acting he must have reasonable ground for believing that the person was of unsound mind

The question for the court was whether this officer acted without reasonable care, for there was nowhere in his affidavit any evidence that the woman was alleged to be of unsound mind Though the doctor was present when she was taken away, he did not appear to have expressed any such view to the officer or to anyone else Whether the officer had in fact acted without reasonable care was a matter to be decided at the trial, but it did not follow that because a person was in a highly excited condition, or a condition of considerable emotional upset, such person was necessarily of unsound mind There was here substantial ground for the contention that the officer acted without reasonable care. The appeal should be dismissed and leave granted to the proposed plaintiffs to proceed

Lord Justice DEVLIN, concurring, said that on the material before the court it was not possible to say whether or not the woman's doctor intended the officer to make a compulsory order The evidence filed for the proposed plaintiffs gave substantial ground for thinking, unless explained or contradicted, that this officer either did not think or could not reasonably have thought that she was a person of unsound mind Though the evidence for the officer set out a different story and contained the matter on which he relied as justifying him in the course he took, it was subject to the extraordinary omission that nowhere did he, or the doctor or anyone else, state the belief that the woman was of unsound mind

A number of suggestions had been put forward to account for that omission One was, that the officer would have inferred from the fact that the doctor asked him to visit the woman's home that the doctor intended him to act under section 20 and that he could therefore properly presume that the doctor had compliance of the lungs is reduced and the non-elastic resistance is increased These changes mean that the work of breathing is increased and this must favour hypoventilation We may therefore have a self-aggravating cycle

hypoventilation→respiratory acidosis→fluid retention→
increased work of breathing→further hypoventilation

We put this hypothesis forward in the hope that work will be stimulated which will prove or disprove it The observations required cover many fields in respiratory, circulatory, endocrine, metabolic, and renal physiology, and the condition of the patients hinders the applicaton of many of the necessary techniques

We also have a practical motive If we are right in thinking that inadequate alveolar ventilation has a central role in the genesis of congestion, more emphasis should be placed on the improvement of ventilation than on the administration of cardiac stimulants and diuretics

SUMMARY

Conventional views of the cause of œdema in " cor pulmonale " are not entirely satisfactory Some or many patients may not pass through the final common pathway of pulmonary hypertension and right ventricular failure

In patients with œdema secondary to respiratory disease of whatever variety, inadequate ventilation and respiratory acidosis are almost always to be found As a cause of fluid retention the respiratory acidosis may be more important than heart-failure One way in which it may cause œdema is suggested

We are particularly indebted to Dr T Simpson for providing us with so much information, and we are grateful both to him and to Dr V Wynn for many helpful comments

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Medicine and the Law

Subpœna by Disciplinary Tribunals

THE departmental committee set up at the beginning of this year, under the chairmanship of Viscount Simonds, to consider the powers of subpœna of disciplinary tribunals, with special reference to evidence obtained by police officers in criminal investigations, has now reported[1] Its main recommendations are

1 Where a disciplinary tribunal has been constituted by statute it should not lack the powers necessary to carry out the duties imposed on it, and among such powers should be the power to secure the issue of writs of subpœna

2 Writs of subpœna should be issuable to secure the production before such tribunals, subject to proper exceptions, of evidence obtained by police officers whether in criminal investigations or otherwise

3 Disciplinary tribunals should have at their disposal legal advice not only for assistance in the conduct of their hearings generally, but for their guidance in ruling on the admissibility of evidence and on claims of privilege

The committee was throughout guided by the principle that in the administration of justice the court or tribunal should have before it all the relevant evidence " Justice cannot be done, nor be seen to be done, if relevant evidence is withheld and is known to be withheld and there is no power to compel it to be given "

The General Medical Council obtained statutory authority to secure the attendance of witnesses before their Disciplinary Committee under the Medical Act, 1950, and the General Dental Council obtained similar authority under the Dentists' Act, 1957 But not all other professional bodies with disciplinary jurisdiction over their members have such express statutory power

The committee (perhaps straying a little beyond its terms of reference) suggests that where a power to obtain the issue of a subpœna is given, there should also be the power to administer the oath to witnesses The committee rejects the suggestions that a writ of subpœna should be issued only at the discretion of a Master of the Supreme Court, and that, if the witness contends that the only evidence that he can give should be excluded on the ground that it would be contrary to the public interest for him to give it, he should have the right to apply to the High Court to set aside the subpœna

As regards police evidence obtained in criminal investigations, the committee declares

" If a domestic tribunal is entrusted with judicial duties which can only be satisfactorily performed if it has before it all the evidence that is relevant and available, and if this condition can only be satisfied by giving it the right to have a subpœna issued, it is clear that the denial of that right in the case of the police or any other potential witness may result in injustice being done "

" If, for instance, a doctor has been convicted of some crime in a criminal court and the question arises before the Disciplinary Committee whether his name should be erased from the Register or some lesser penalty imposed, it may be of the utmost materiality to know the circumstances of the offence of which the police alone have knowledge This will particularly be the case where he has pleaded guilty before the criminal court and little evidence has been given Equally there may be a case in which the accused has been found not guilty of the crime with which he has been charged, but the evidence given by the police has shown at least a *prima facie* case that he had been guilty of disgraceful conduct in a professional sense "

Generally speaking, the subpœna should be issuable and the police officer at the hearing should plead Crown privilege if so directed But in a wide field no plea of Crown privilege would be available

For instance, in a criminal investigation the police officer may witness conduct which, though falling short of crime, is disgraceful in a professional sense " he may be invited or allowed to 'listen in' to a telephone conversation and so be able to corroborate the evidence of the listener about something said by the speaker In such cases we see no reason why he should not be required to give evidence on *subpœna* It would in our opinion be intolerable if the course of justice was defeated by the withholding of evidence in such cases "

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[1] Report of the Departmental Committee on Powers of Subpœna of Disciplinary Tribunals Cmnd 1033 H M Stationery Office Pp 18 1s

Disciplinary tribunals, the committee concludes, perform a valuable function for the benefit of the public, and it is the duty of all authorities and persons, whether in uniform or not, to assist them to the best of their ability

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Lord Justice **Devlin**, concurring, said that on the material before the court it was not possible to say whether or not the woman's doctor intended the officer to make a compulsory order The evidence filed for the proposed plaintiffs gave substantial ground for thinking, unless explained or contradicted, that this officer either did not think or could not reasonably have thought that she was a person of unsound mind Though the evidence for the officer set out a different story and contained the matter on which he relied as justifying him in the course he took, it was subject to the extraordinary omission that nowhere did he, or the doctor, or anyone else, state the belief that the woman was of unsound mind

A number of suggestions had been put forward to account for that omission One was,that the officer would have inferred from the fact that the doctor asked him to visit the woman's home that the doctor intended him to act under section 20 and that he could therefore properly presume that the doctor had be given special privileges, nor granted consultations on treatment with medical staff They hope that hospital management committees who have already given their permission for official visits will reconsider their decisions

Regional Hospitals Consultants
and Specialists Association,
47, Lincoln s Inn Fields,
London, W C 2

V COTTON CORNWALL
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FLUORIDATION

SIR,—It is an entirely new departure in the practice of medicine to advocate the mass dosing of the entire population with a highly toxic substance without the consent, and in many cases against the very active opposition, of the subject, Since the dosage depends on the amount of water consumed in drinking and cooking, and takes no account of the many other sources of fluorine intake nor of possible individual hypersensitivity, it is a grossly unscientific procedure Moreover, as Dr Dobbs (April 2) pointed out, the evidence for the complete safety of fluoridation is inadequate

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SIR,—May I suggest to Dr Dalzell-Ward (May 21), of the Central Council for Health Education, that he and his Council would be better employed advocating a reduction or abolition of the duty levied on cigars and pipe tobacco? By thus encouraging the smoking of pipes and cigars instead of cigarettes an administrative measure might achieve a substantial reduction in the incidence of carcinoma of the lung

Would the reduction of lung cancer be of greater value to society than the reduction of dental decay? I defy even so eminent an authority as Dr Dalzell-Ward and his Council to answer that one in the negative

Incidentally, Dr Dalzell-Ward's figures support the contention to which I do subscribe—namely, that there is a case for fluoridating children for a limited period of years rather than the entire population all the time I would, for example, be extremely interested in seeing the effect of fluoridating school milk and various of the "fruit" drinks popular with children

Salisbury

HUGH V CAPSTICK

THE PRESS, THE PATIENT, AND THE HOSPITAL DOCTOR

SIR,—Dr White Franklin's observations (May 14) on cooperation with the Press by hospital medical staffs make interesting Experience has proved that cooperation with the Press on such occasions as he describes will avoid the confusion and mutual antagonism which can occur if the hospital pursues a policy of silence If the hospital flatly refuses to give the Press any information at all, then clearly if they are reporting a matter considered to be of public interest they will be obliged to get their information by less conventional means, which can only cause bad relations among all concerned

All this was firmly borne in mind by the Conference of the Medical Profession and the Press which met at B M.A. House during 1955 This conference consisted of representatives of the national and provincial Press, and the B B C, on the one side, and, on the other, representatives of the B M A and the Joint Consultants Committee I had the honour to be chairman of this conference

This conference produced a report on a recommended routine procedure for dealing with the Press in hospitals In this it was suggested that "all hospitals should ensure *that a sufficiently experienced and responsible officer* of the hospital is at all times available, whether in person or by telephone, to answer press enquiries, and should nominate an officer or officers for this purpose" (This memorandum was later issued by the Ministry of Health as a circular to all hospitals in the United Kingdom)

In his article Dr Franklin mentions a "hue and cry" at St Bartholomew's which lasted two days and "which should not have occurred" May I suggest that the hue and cry *would* not have occurred had the routine procedure recommended by the conference been adopted

British Medical Association,
Tavistock Square,
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H GUY DAIN

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SIR,—I am grateful to Dr Guy Dain for his comments The "hue and cry" was in the Press and not at St Bartholomew's Hospital The news would have been less dramatic had we had a statement ready for circulation as soon as we knew of Press interest Such a statement should always be prepared by the medical staff in consultation with the administrative staff Whether a special hospital officer is really needed for this purpose is certainly a question worth discussing The answer would not automatically be an affirmative one

London, W 1

ALFRED WHITE FRANKLIN

TREATMENT OF SALICYLATE POISONING

SIR,—Your annotation of April 23 quotes a suggestion by Rentsch et al [1] that in children a plasma-salicylate of 40 mg per 100 ml is a critical level, over which exchange transfusion should be considered We should be interested to know whether expert opinion in this country would support that suggestion, for our impression is that it might lead to a number of unnecessary exchange transfusions, with their potential hazards

It is only fair to note that Rentsch and her associates based their opinion on a review of some published case-reports rather than on their own experience, for the two patients treated by them in this way, boys of 2 and 3 years, had plasma salicylate levels of 79 and 69 mg per 100 ml respectively before, and 48 and 39 mg per 100 ml respectively after, exchange The youngest case of salicylate poisoning we have seen was a boy aged 23 months who recovered rapidly from a plasma-salicylate of over 60 mg per 100 ml under treatment along orthodox (but conservative) lines In older children and adults receiving salicylates for rheumatic fever and other diseases we have not encountered serious toxic effects at serum-salicylate concentrations below 55 mg per 100 ml, but it is likely that in babies much lower levels would be dangerous, for several reasons[2,3] It is obvious (as Rentsch et al admit) that the decision to treat by exchange transfusion or hæmodialysis must depend on factors other than plasma-salicylate values, age, clinical assessment, time interval since ingestion of salicylate, rapidity of onset of toxic signs, degree of metabolic and electrolytic disorder, and response to other forms of therapy are all important.

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[1] Rentsch J B, Bradley, A, Marsh, S B *A M A J Dis Child* 1959, 98, 778

Dr Frank Wilson's letter (May 14) raises another pertinent question—namely, the anæsthetist's potential contribution to treatment of salicylate poisoning—and we think many physicians would value the cooperation of an anæsthetist in such cases We have some reservations, however, concerning the efficacy of curarisation in reducing hyperpyrexia caused by salicylate, for Tenney and Miller[4] have shown that in dogs the well-known metabolic-stimulant action of salicylate,[5] although located mainly in skeletal muscle, is undiminished by curare, it is this increase in metabolism which is largely responsible for the hyperpyrexia[6] May we suggest that the drugs used by anæsthetists in induction of hypothermia might be useful adjuvants in treatment of the hyperpyrexia?

Stobhill General Hospital, Glasgow

A I MACDOUGALL
D J C CAMERON

OTOTOXICITY OF NEOMYCIN AEROSOL

SIR,—The two patients reported by Mr Fuller (May 7) are part of a series of cases of cystic fibrosis of the pancreas, many of which have been treated with neomycin aerosol at the Queen Elizabeth Hospital for Children Owing to the severity of their bronchiectasis they and one other patient have received intensive treatment for much longer than the rest and they are the only ones who have become deaf The two reported cases have both succumbed to their respiratory disease during the course of this winter

In collaboration with my otologist colleagues I have now been able to reassure myself that neomycin aerosol can be used for many months without risk of ototoxicity The work in support of this opinion will be published in due course

My object in writing is to offset the implication of Mr Fuller's letter, which might lead clinicians to avoid the use of therapy which often proves more effective than any other in controlling the staphylococcal bronchitis to which children with cystic fibrosis of the pancreas are especially prone

Queen Elizabeth Hospital for Children, Hackney Road, London, E.2.

WINIFRED F YOUNG

HÆMOGLOBIN STANDARD

SIR,—The letters by Dr Stallybrass (April 16 and May 7) and Dr Hendry (May 7) deal with what is certainly one of the principal problems of contemporary biology—technical standardisation

It is obvious that "no Commission can standardise the iron content of hæmoglobin" but a Commission could help scientists by drawing their attention to facts such as those mentioned by Dr Hendry and also, by recommending the use of standard methods, techniques, and apparatus in such disciplines as cytology, hæmatology, biochemistry, and physiology on an international scale

This is the aim of the International Committee for Standardisation in Human Biology (I C S H B), which was founded in 1958 and which has at the present time some 200 members (mainly professors in State universities) from 35 countries The first general conference of I C S H B will be held in Unesco on July 30, 1960

From time to time, individual and even national susceptibilities will certainly complicate this task, but we hope that finally scientists will perceive the urgent necessity of achieving a balance between the individual process of invention and the social process of standardisation

Hopital Cochin, Paris

P M DE TRAVERSE

PERTHES' DISEASE

SIR,—I am afraid I remain quite unrepentant in spite of the list of authorities quoted by Professor Trueta (April 2) I have not been able to discuss this with Dr Cockshott of Ibadan but I think it is unlikely that his opinion will alter either May I explain some of the problems and try and put the matter in its correct perspective?

Firstly, there is no doubt at all that Perthes' disease is seen in the African in this part of Southern Rhodesia There is one typical and active case in the Mpilo Hospital at present, and both I and the orthopædic surgeons concerned can clearly remember others it had not occurred to us that it was a rare condition and we have not therefore indexed each case as it was seen The fact that it has not been reported from a place such as Uganda or in other Negro children is, I fear, quite irrelevant To take another example one of the commonest types of malignant disease seen here in Africans in Bulawayo is carcinoma of the œsophagus Dr Cockshott will agree with me that in Ibadan in Nigeria it is relatively uncommon Again it has been stated that carcinoma of the bronchus is rare attention was drawn to this in the report of the planning committee discussing the proposed Medical School in Salisbury Although less than 300 miles away, we here in Bulawayo would not agree that carcinoma of the bronchus is uncommon in the African We saw at least 80 cases in the last 12 months Similar statements have been made about duodenal ulcer and carcinoma of the stomach and have been proved to be quite erroneous In other words it is very unwise to consider that any disease is rare in the Negro (or the African) without considering all the other aspects of locality, race, tribe, occupation, etc, and including information on the medical services available no-one working without an X-ray set can be expected to diagnose Perthes' disease with any accuracy

It is simply not possible to make a sweeping statement about "Africa" It is obvious that there are vast geographical differences and the sooner these are correlated and explored the better

The other great difficulty in Africa is the patient himself There can be very few cases of Perthes' disease in which the young African has sufficient pain to make him go to hospital, there are a large number of patients who are seen with the last stages of damaged hips, many of whom had Perthes' disease originally and did not report It is true that it is difficult to be certain whether all these hips result from Perthes' disease because some will have resulted from a slipped epiphysis or any other type of damage or even infection It is well nigh impossible to produce accurate figures concerning the frequency of Perthes' disease for this reason The same argument does not apply to a condition such as carcinoma of the œsophagus in which, because it is impossible to swallow, the patient reports to hospital It does apply to a great many other conditions, even tuberculous spines, osteomyelitis, &c., which are only seen when the condition is so advanced that it is, by European standards, virtually unrecognisable and almost untreatable

From this it will be seen that we cannot produce accurate

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[2] Hoffman W S *ibid* 1953, 85 58
[3] Riley, H D Worley L *Pediatrics* 1956 18, 578
[4] Tenney, S M Miller, R M *Amer J Med* 1955 19 498
[5] Cochran J B *Brit med J* 1952, ii 964
[6] Reid J *Scot med J* 1957, 2, 91

tension" in middle age the rate of increase of diastolic pressure rose from 0 64 mm per year in the normotensive phase to 5 9 in the hypertensive phase This is strong evidence of a qualitative difference, and surely makes nonsense of methods which only show average behaviour pooled for the whole population.

6 Age and sex scores depend on the acceptance of continuous distribution and average behaviour and therefore cannot help in this controversy

7 The methods of the Pickering group seem to me just those which could best conceal the existence of two populations if in fact they do exist (which I have never claimed to have proved) The "new" concept of Essential Hypertension, far from "stimulating inquiry", stifles it at birth

8 A statement[6] on p 1092 seems to impute to me the idea that a single gene could account for all the factors which together determine blood-pressure As I have already pointed out,[7] I do not believe that it could But of course this does not rule out the possibility that a single determinant could upset the balance and cause hypertension (as it does for instance in aldosteronism or phæochromocytoma)

University Department of Medicine,
Royal Infirmary,
Manchester 13
ROBERT PLATT

FATTY FOODS AND OBESITY

SIR,—We have read with interest the papers of Dr Pilkington and his colleagues (April 16) and Dr Olesen and Dr Quaade (May 14) which confirm our observations that over a short period of time the composition of the diet affects the rate and degree of weight change We ourselves have never claimed any particular therapeutic benefit from the high-fat regime in the long-term treatment of the obese, and indeed have been at some pains in your columns to disclaim responsibility for this idea,[8] and have more recently pointed out that such a regime may have undesirable side-effects[9] Such diets may, however, have some effects on appetite and satiety, even in the long term

We have, of course, been aware of the adaptation mechanism alluded to in the two papers, and indeed a paper from this department on the subject was read to the Physiological Society by Dr S B Furnass last year, and we hope this will be published shortly

The only point over which we are in disagreement with both groups of authors is that they have fallen back on to the old argument that the different short-term effects of these diets must be to increase or decrease total body-water, since no other acceptable explanation offers itself Unfortunately, water-balance studies provide no information on this point If there is weight-loss in a subject as a result of dieting, then it can be produced by diminishing the amount of total body-water, whether "free" or "bound", or from burning tissue, since 100 grammes of fat yields approximately 100 ml of water, while protein and carbohydrate give half this figure Information as to which of these has taken place can only be obtained by measuring total body-water, and it is a pity that neither group has attempted this We ourselves started with the belief that these weight changes arose only from alterations in body-water, but, as a result of experimental observations, have had to change this view, and at present believe that they are brought about in part by changes in metabolism which have resulted in different rates of tissue catabolism

A letter to your journal is not the place for lengthy discussion of the evidence, but we would like to outline the following five points to substantiate our present position

(i) When total body-water was measured at the beginning and end of a period of weight change produced by our different isocaloric diets, changes in the measurable body-water did not account for the whole of the weight change as it does, for example, when the same measurements are made in patients undergoing treatment for cardiac failure We would agree with Olesen and Quaade's contention that the methods leave something to be desired, but until better methods and more information are available, we have had to accept this conclusion

(ii) The different diets used by us produced measurable changes in insensible loss in many subjects This has been confirmed by others and the implication of these findings discussed in our previous papers[10 11]

(iii) 1000-calorie diets supplied in the form of 90% fat or 90% protein both result in subjects producing a substance in the urine which will mobilise fatty acids from adipose tissue in vitro and cause loss of carcass fat when injected into mice The same subjects on a 1000-calorie diet supplied as 90% carbohydrate for periods up to two weeks do not produce detectable amounts of this substance[12 13]

(iv) It has been shown in this department that the metabolic response of obese subjects to a fixed dextrose or fat load in terms of 24-hour respiratory quotients differs according to the previous dietary intake[14]

(v) High-fat feeding in animals inhibits the ability of adipose tissue to synthesise fat from carbohydrate[15]

Although we disagree with both groups of authors over this important point, the publication of these two studies is a welcome sign of an awakening interest in some of the unsolved metabolic problems occurring during the development and treatment of obesity

Department of Medicine,
The Middlesex Hospital,
London, W 1
A KEKWICK
G L S PAWAN

HUMAN RELATIONS IN OBSTETRIC PRACTICE

SIR,—I listened to Professor Norman Morris's lecture with interest and enthusiasm, and I have read the abbreviated form which appeared in *The Lancet* on April 23 The patients' views at the lecture itself were delivered by themselves on a tape recording, which made them very convincing indeed

The point that Professor Morris makes, that some hospitals do not pay enough attention to the psyche of the pregnant and parturient woman, is one that very much needed making, and it was pressed home in the lecture Confirmation of the facts has been provided in the correspondence appearing since

It is unfortunate that criticism of other people is usually so much more tasty to the reader than approbation of what they do

In these days patients know much more about what service they should get and many hospitals appreciate the importance of keeping them contented and well-informed as well as healthy during pregnancy and after I would say that the importance of this has never been more realised by doctors and midwives than at present, and I know that expressions of gratitude from the consumers frequently reaches them This needs to be said and realised It would be a pity if people were left with the idea that this work ought to be carried out by the professions concerned but was being totally neglected by them

Professor Morris's chastisement should fall on some of those who supervise labour in domiciliary patients also There was a letter relevant to this published in *The Guardian* in late February of this year

Department of Obstetrics
and Gynæcology,
University of Leeds
ANDREW CLAYE

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[6] Oldham, P D Pickering, G W, Roberts, J A F, Sowry, G S C *ibid* 1960, i, 1085

[7] Platt, R *ibid* 1959, ii, 1092

[8] Kekwick, A, Pawan, G L S *ibid* 1958, ii 908

[9] Kekwick, A, Pawan, G L S, Chalmers, T M *ibid* 1959, ii, 1157

[10] Kekwick, A Pawan, G L S *ibid* 1956, ii, 155

[11] Kekwick, A, Pawan, G L S *Metabolism* 1957, 6, 447

[12] Chalmers, T M, Kekwick, A, Pawan, G L S, Smith, I *Lancet*, 1959, i, 866

[13] Chalmers T M, Pawan G L S, Kekwick, A *ibid* (in the press)

[14] Furnass, S B *J Physiol* 1960 150 11P

[15] Hausberger, F X, Milstein, S W *J biol Chem* 1955, 214 483

SIR,—I have no doubt Professor Morris has some good reason for publishing his views however erroneous some of them may be A great deal of lip service is paid to what is called "human relationships" It is hard to understand why Professor Morris or your other correspondents think they can help the interest or the welfare of the mother and the baby by decrying and disparaging the midwife

The medical, nursing, and midwifery professions are all dependent on each other for their success in the care of patients, but it is profoundly disturbing to have the recent publicity which will have far-reaching effects on recruitment of nurses and midwives

Parents of young would-be nurses and midwives will think again before allowing their daughters to train, thus increasing the shortage of nursing staff and increasing the burden on our already overloaded personnel

May I quote the words of William Smellie, written about 1751, speaking of the midwife

> "She ought to live in friendship with other women of the same profession, contending with them in nothing but in knowledge, sobriety, diligence and patience, she ought to avoid all reflections upon men practitioners, and when she finds herself at a loss, candidly have recourse to their assistance This confidence ought to be encouraged by the man who ought to rectify what is amiss without exposing her mistakes These gentle methods will prevent that mutual calumny and abuse which too often prevail among the male and female practitioners, and (will) redound to the advantage of both, for no accoucheur is so perfect but that he may err sometimes "

Watford Maternity Hospital NORA K KELLY

SIR,—I was most interested in the letters of Mr Blackwell and Dr Nora Wilkinson in your issue of May 21 I wonder whether it will ever be possible to persuade obstetricians, other doctors, and midwives that every patient that comes under their care is a human soul very often about to undergo a very anxious experience for the first time, not just one more case to be put on the conveyor belt to go through the routine procedure in, we hope, the usual time

I have now been long enough in the practice of the medical art to notice with great regret this gradual replacement of the human personality with a Case No In fact not so long ago when a patient in hospital myself I was referred to as Case No 20

Surely a little time spent during the antenatal period explaining to both husband and wife what to expect and how they can help would reap a rich reward But there again, as I have so often said before, there is that Time Factor

Worthing HAROLD LEESON

SIR,—I am writing to join in welcoming Professor Morris' article

In terms of human relationships the influence of the antenatal clinic is reflected in a statistical study[1] of two groups of physically normal primiparæ The study correlates antenatal attendances with the incidence of breast-feeding group I with more than 9 antenatal attendances showed a statistically significant higher incidence of breast-feeding and a lower incidence of unexplained milk failures than the second group with few antenatal attendances

A possible interpretation is that women and antenatal clinics able to form stable working relationships do better in establishing lactation In social, physical, or psychological terms we have little accurate appraisal of the factors involved in the establishment of the relationship between a woman and her antenatal clinic.

Clinical psychiatric work with puerperal cases suggests that not only are a woman's resources, in past experience, an important determinant in how she will behave in motherhood, but how she comes to experience herself as being cared for in the present is also important, particularly when the present can link with and resolve anxieties from the past As shown by the letters Professor Morris quotes, being sent home with a live baby may be tolerated, but isn't enough

Professor Morris stresses the importance of preparatory classes in antenatal care It is here I would suggest that there is also the possibility of making a beginning in investigating and facilitating a woman's relationship with her clinic This might be done through adapting and employing some of the techniques and experiences gained with psychiatric groups This is where dynamic psychology, which Dr Abraham (April 20) rightly stresses as being so important, could make an immediate and appropriate contribution

I agreee with Professor Morris in emphasising the importance of so-called normal obstetrics, but only when there is the opportunity of trying to understand each woman as an obstetric individual can we discard "the rules of thumb" and do without the support of "a conveyor-belt system" This brings us back to our own interest in the question, how is the woman achieving and establishing her motherhood, and to the need for further study in attempting to answer it responsibly

The Cassel Hospital for
Functional Nervous Disorders,
Richmond, Surrey A R WILSON

SPIRITUAL HEALERS IN HOSPITAL

SIR,—Our attention has been called to the fact that the National Federation of Spiritual Healers has been granted access to some hospitals, by the management committees concerned, for the purpose of treating patients

In *The Times* of April 18 the Bishop of Lichfield stated that

> "The admission of 'Spiritual Healers' to hospital wards raises matters of considerable concern which have now been considered at a meeting of the Executive Committee of the Churches' Council of Healing This Council is the official representative body of both the medical profession and of the Christian communions in England, Scotland, Wales and Ireland, which are associated with the British Council of Churches The medical profession is represented on it by doctors appointed by the British Medical Association, the Royal College of Physicians, the Royal College of Surgeons, the Royal College of Obstetricians and Gynæcologists, the Royal Medico-Psychological Association, the Society of Medical Officers of Health, and the College of General Practitioners The Royal College of Nursing also have representatives on our Council My purpose now is to point out that the National Federation of Spiritual Healers which is seeking to introduce its members officially into hospitals for the purpose of spiritual healing is not recognised by my Council"

The National Federation of Spiritual Healers state that in some cases they treat patients by suggestion after the laying on of hands, and demonstrations of this technique were given by Mr Harry Edwards at a meeting at the Royal Festival Hall on April 30

The responsibility for treatment of patients is vested in the consultants appointed by regional hospital boards and boards of governors, and it is unethical in a medical sense for doctors to "cover" unqualified practitioners It is essential that the doctors concerned should satisfy themselves that in giving consent to members of this Federation to visit their patients they are not laying themselves open to the charge of "covering"

It is not suggested that an adherent of any faith should be debarred from receiving any visitor of his choice in a private capacity, and indeed valuable help has been afforded to many patients by their spiritual advisers

My council was unanimous in advising that members of the National Federation of Spiritual Healers should not be given special privileges, nor granted consultations on treatment with medical staff They hope that hospital management committees who have already given their permission for official visits will reconsider their decisions

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[1] Maternity in Great Britain, ch 12 London, 1948

Regional Hospitals Consultants
and Specialists Association,
47, Lincoln s Inn Fields,
London, W C 2
V COTTON CORNWALL
President.

FLUORIDATION

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Darlington
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All this was firmly borne in mind by the Conference of the Medical Profession and the Press which met at B M A House during 1955 This conference consisted of representatives of the national and provincial Press, and the B B C, on the one side, and, on the other, representatives of the B M A and the Joint Consultants Committee I had the honour to be chairman of this conference

This conference produced a report on a recommended routine procedure for dealing with the Press in hospitals In this it was suggested that "all hospitals should ensure that a sufficiently experienced and responsible officer of the hospital is at all times available, whether in person or by telephone, to answer press enquiries, and should nominate an officer or officers for this purpose" (This memorandum was later issued by the Ministry of Health as a circular to all hospitals in the United Kingdom)

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London, W C 1
H GUY DAIN

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London, W 1
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TREATMENT OF SALICYLATE POISONING

SIR,—Your annotation of April 23 quotes a suggestion by Rentsch et al [1] that in children a plasma-salicylate of 40 mg per 100 ml is a critical level, over which exchange transfusion should be considered We should be interested to know whether expert opinion in this country would support that suggestion, for our impression is that it might lead to a number of unnecessary exchange transfusions, with their potential hazards

It is only fair to note that Rentsch and her associates based their opinion on a review of some published case-reports rather than on their own experience, for the two patients treated by them in this way, boys of 2 and 3 years, had plasma-salicylate levels of 79 and 69 mg per 100 ml respectively before, and 48 and 39 mg per 100 ml respectively after, exchange The youngest case of salicylate poisoning we have seen was a boy aged 23 months who recovered rapidly from a plasma-salicylate of over 60 mg per 100 ml under treatment along orthodox (but conservative) lines In older children and adults receiving salicylates for rheumatic fever and other diseases we have not encountered serious toxic effects at serum-salicylate concentrations below 55 mg per 100 ml, but it is likely that in babies much lower levels would be dangerous, for several reasons.[2,3] It is obvious (as Rentsch et al. admit) that the decision to treat by exchange transfusion or hæmodialysis must depend on factors other than plasma-salicylate values, age, clinical assessment, time interval since ingestion of salicylate, rapidity of onset of toxic signs, degree of metabolic and electrolytic disorder, and response to other forms of therapy are all important.

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[1] Rentsch, J B, Bradley, A, Marsh, S B *A M A J Dis Child* 1959, 98, 778

Dr Frank Wilson's letter (May 14) raises another pertinent question—namely, the anæsthetist's potential contribution to treatment of salicylate poisoning—and we think many physicians would value the cooperation of an anæsthetist in such cases. We have some reservations, however, concerning the efficacy of curarisation in reducing hyperpyrexia caused by salicylate, for Tenney and Miller[4] have shown that in dogs the well-known metabolic-stimulant action of salicylate,[5] although located mainly in skeletal muscle, is undiminished by curare, it is this increase in metabolism which is largely responsible for the hyperpyrexia.[6] May we suggest that the drugs used by anæsthetists in induction of hypothermia might be useful adjuvants in treatment of the hyperpyrexia?

Stobhill General Hospital,
Glasgow

A I MACDOUGALL
D J C CAMERON

OTOTOXICITY OF NEOMYCIN AEROSOL

SIR,—The two patients reported by Mr Fuller (May 7) are part of a series of cases of cystic fibrosis of the pancreas, many of which have been treated with neomycin aerosol at the Queen Elizabeth Hospital for Children. Owing to the severity of their bronchiectasis they and one other patient have received intensive treatment for much longer than the rest and they are the only ones who have become deaf. The two reported cases have both succumbed to their respiratory disease during the course of this winter.

In collaboration with my otologist colleagues I have now been able to reassure myself that neomycin aerosol can be used for many months without risk of ototoxicity. The work in support of this opinion will be published in due course.

My object in writing is to offset the implication of Mr Fuller's letter, which might lead clinicians to avoid the use of therapy which often proves more effective than any other in controlling the staphylococcal bronchitis to which children with cystic fibrosis of the pancreas are especially prone.

Queen Elizabeth Hospital for Children,
Hackney Road, London E.2

WINIFRED F YOUNG

HÆMOGLOBIN STANDARD

SIR,—The letters by Dr Stallybrass (April 16 and May 7) and Dr Hendry (May 7) deal with what is certainly one of the principal problems of contemporary biology—technical standardisation.

It is obvious that "no Commission can standardise the iron content of hæmoglobin" but a Commission could help scientists by drawing their attention to facts such as those mentioned by Dr Hendry and also, by recommending the use of standard methods, techniques, and apparatus in such disciplines as cytology, hæmatology, biochemistry, and physiology on an international scale.

This is the aim of the International Committee for Standardisation in Human Biology (I.C.S.H.B.), which was founded in 1958 and which has at the present time some 200 members (mainly professors in State universities) from 35 countries. The first general conference of I.C.S.H.B. will be held in Unesco on July 30, 1960.

From time to time, individual and even national susceptibilities will certainly complicate this task, but we hope that finally scientists will perceive the urgent necessity of achieving a balance between the individual process of invention and the social process of standardisation.

Hopital Cochin, Paris

P M DE TRAVERSE

PERTHES' DISEASE

SIR,—I am afraid I remain quite unrepentant in spite of the list of authorities quoted by Professor Trueta (April 2). I have not been able to discuss this with Dr Cockshott of Ibadan but I think it is unlikely that his opinion will alter either. May I explain some of the problems and try and put the matter in its correct perspective?

Firstly, there is no doubt at all that Perthes' disease is seen in the African in this part of Southern Rhodesia. There is one typical and active case in the Mpilo Hospital at present, and both I and the orthopædic surgeons concerned can clearly remember others; it had not occurred to us that it was a rare condition and we have not therefore indexed each case as it was seen. The fact that it has not been reported from a place such as Uganda or in other Negro children is, I fear, quite irrelevant. To take another example: one of the commonest types of malignant disease seen here in Africans in Bulawayo is carcinoma of the œsophagus. Dr Cockshott will agree with me that in Ibadan in Nigeria it is relatively uncommon. Again it has been stated that carcinoma of the bronchus is rare: attention was drawn to this in the report of the planning committee discussing the proposed Medical School in Salisbury. Although less than 300 miles away, we here in Bulawayo would not agree that carcinoma of the bronchus is uncommon in the African. We saw at least 80 cases in the last 12 months. Similar statements have been made about duodenal ulcer and carcinoma of the stomach and have been proved to be quite erroneous. In other words it is very unwise to consider that any disease is rare in the Negro (or the African) without considering all the other aspects of locality, race, tribe, occupation, etc., and including information on the medical services available: no-one working without an X-ray set can be expected to diagnose Perthes' disease with any accuracy.

It is simply not possible to make a sweeping statement about "Africa". It is obvious that there are vast geographical differences and the sooner these are correlated and explored the better.

The other great difficulty in Africa is the patient himself. There can be very few cases of Perthes' disease in which the young African has sufficient pain to make him go to hospital; there are a large number of patients who are seen with the last stages of damaged hips, many of whom had Perthes' disease originally and did not report. It is true that it is difficult to be certain whether all these hips result from Perthes' disease because some will have resulted from a slipped epiphysis or any other type of damage or even infection. It is well nigh impossible to produce accurate figures concerning the frequency of Perthes' disease for this reason. The same argument does not apply to a condition such as carcinoma of the œsophagus in which, because it is impossible to swallow, the patient reports to hospital. It does apply to a great many other conditions, even tuberculous spines, osteomyelitis, &c., which are only seen when the condition is so advanced that it is, by European standards, virtually unrecognisable and almost untreatable.

From this it will be seen that we cannot produce accurate

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[2] Hoffman W S [illegible] 1953 85 58
[3] Riley H D Worley, L *Pediatrics* 1956 18 578
[4] Tenney, S M, Miller, R M *Amer J Med* 1955 19, 498
[5] Cochran J B *Brit med J* 1952 ii, 964
[6] Reid J *Scot med J* 1957, 2, 91

figures of Perthes' disease in the African, I am, however, quite convinced that it occurs frequently and that as the African advances in civilisation will be seen in hospitals at an earlier stage and more commonly Whether this will be true of all Negro races is quite another matter

Mpilo Hospital, Bulawayo
P E S Palmer

AN EASIER ALPHABET

Sir,—May I thank Dr Thomas (May 14) for explaining so clearly the difference between "redundancy" and "noise"? He is entirely correct in saying the patients in the group described (April 23) were unable to exclude noise from signal and had a low signal/noise ratio

If we were speaking of a radio set instead of a human brain we would say simply that it was a very noisy set Is it helpful to say similarly, a schizophrenic has a very noisy brain or is it merely providing a new name for a very old condition? In my view it is a great step forward for two reasons

Firstly, because it raises the question which part of the "machine" is the "noise" coming from? In the group of patients referred to the "noise" or "irrelevant information" was being picked up along with the message and transmitted unchanged This is very different from "noise" generated in the "machine" such as an hallucination

The second reason is that once you know in terms of information theory, such as "signal/noise ratio", what you are trying to measure it is relatively easy to design a machine to give a graduated score Then by retesting a patient one can say unequivocally whether a particular treatment is causing this abnormality to become more or less marked The somewhat crude machine I used at Rampton State Hospital some five years ago to obtain a graduated score consisted of a recessed form board into which sixty flat shapes could be placed There were only two types of "shape" but the form board and "shapes" were covered by bands of many different colours If any piece was placed to match colour (contrary to instructions) it closed electrical contacts in the form board and recorded a score on a recording device Such measurements are perhaps unnecessary in following the progress of frank psychotics with clear-cut symptoms They are, however, very useful in the quasi-psychotic with a history of an isolated bizarre act in which symptoms are often few and vague

A young man with a record of stable conduct and regular employment awoke one night and, after loading his gun, entered his employer's house and went to the bathroom where he stripped He then donned some female underclothing, retreated to an empty bedroom, rested his gun on a chair, and waited for someone to enter His employer coming to investigate the noise was shot as he opened the door By the time the young man reached hospital some months later he had no frank psychotic or neurotic features, could give no explanation, but maintained he had always and still liked his employer

In such cases it is difficult to know when a patient is fit for discharge A change in signal/noise ratio from grossly abnormal to normal limits is in my view a valuable addition to the normal psychiatric intuition which frequently governs such decisions

Whittingham Hospital,
near Preston
S L Pugmire

CHROMOSOMES IN MARFAN'S DISEASE

Sir,—Recently Puck et al[1] described one chromosome with giant satellites in each of two patients labelled as cases of familial Marfan's disease They state that "while the present data do not prove the given abnormalities to be the underlying cause of Marfan's syndrome, a relationship is definitely suggested" This fascinating observation must be pursued in clinically well-studied cases The cytological demonstrations are convincing However, for several reasons it seems very unlikely that there is a gross and specific chromosomal aberration of this type in the Marfan syndrome

(1) Most importantly, it is by no means certain that the two cases with satellite peculiarities had the true Marfan syndrome In neither was ectopia lentis noted One had tricuspid atresia and atrial and ventricular septal defects—a complex of cardiac malformations quite unknown in the Marfan syndrome The other, an 18-month-old infant, had only skeletal features which are notoriously unreliable as the sole basis of the diagnosis Although extensive pedigrees of the two cases are shown, in one "the genealogy was established from the patient's hospital record" and "no other members of this patient's family are available for study" In the second family the pedigree chart was apparently assembled only by hearsay "from questioning of members of the patient's family, who have been very cooperative" No indication is provided that any of the family members said to be affected had ectopia lentis or aneurysm of the aorta with aortic regurgitation, less disputable manifestations of the Marfan syndrome It is stated that "this condition is a relatively poorly characterised clinical situation" On the contrary, its nosography had advanced to a quite high plane[2] The clinical picture is admittedly varied but is no more variable than, for example, that produced by many specific microorganisms

(2) In the same report the authors describe a case of obviously bona-fide Marfan syndrome with ectopia lentis, skeletal changes, and a heart lesion That the case was sporadic is no necessary indication that it was basically different from familial cases of the true syndrome This one acceptable case of the Marfan syndrome did not have a satellite peculiarity

(3) In the two cases with satellite peculiarities, chromosome 21 was affected in one and chromosome 18 in the other Although heterogeneity may well exist in the Marfan category, this lack of consistency weakens the hypothesis of a specific relationship

(4) Such giant satellites are occasionally seen in patients without stigmata of the Marfan syndrome[3]

(5) Ford[4] and Book's group[5] have examined the chromosomes in cases of the Marfan syndrome without detecting this abnormality, which to be sure could perhaps have been overlooked

As stated above, the cytologic observations can scarcely be questioned Furthermore, in the two patients, the peculiarity described may bear a causal relationship to the malformations present in each However, that the satellite peculiarity is the specific underlying cause of the Marfan syndrome is doubtful

Division of Medical Genetics,
Department of Medicine,
Johns Hopkins University
School of Medicine,
Baltimore, Maryland
Victor A McKusick

IMMUNE TOLERANCE IN MOTHER AND FŒTUS

Sir,—Embryologists will wish to take issue with Dr Gordon (May 14) concerning his views on the origin of placental syncytiotrophoblast This tissue cannot possibly originate from granulosa cells as suggested because of the following reasons

In the ovarian follicle the oocyte is surrounded by a zona pellucida that separates it from the other cells constituting the follicle. After ovulation and later fertilisation, the zona pellucida still separates the ovum from the cells of the corona radiata During the early progestational phases of development trophoblastic cells already start to develop inside the zona pellucida, and the latter has to disintegrate or give way, to allow implantation to be effected by the early trophoblast

I have recently obtained confirmatory, experimental evidence that, at any rate in the rabbit, both cyto- and syncytio-trophoblast originate from the blastocyst The experiments I refer to consist in procuring the implantation of blastocysts in endometrium incubated as organ cultures. If this procedure is to be successful, it is necessary to dissect off the zona pellucida before placing the blastocysts on the endometrium. This precludes any chance of granulosa cells being included in the explant, yet I can assure Dr Gordon that both cyto- and syncytiotrophoblast develop in the cultures and that the trophoblast shows definite invasive tendencies.

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[1] Tjio, J H, Puck, T T, Robinson, A *Proc Nat Acad Sci* 1960 46, 532

[2] McKusick, V A *Heritable Disorders of Connective Tissue* St Louis, 1956 and 1960

[3] Ferguson-Smith, M A Personal communication

[4] Ford C E *Amer J hum Genet* 1960 12, 104

[5] Book, J A, Fraccaro, M, Lindsten, J Cited by Ford (ref 4)

Department of Anatomy,
Charing Cross Hospital Medical School,
London, W C 2

T W GLENISTER

MATERNAL INFLUENZA AND CONGENITAL DEFORMITY

SIR,—Dr Acheson's comments (April 30) on the investigation by Dr Coffey and Professor Jessop are very much to the point, as well as being pointed, albeit in the wrong direction. His statements will help to dispel and dissipate some of the obfuscation and obnubilation that often surround clinical investigations which present conflicting opinions.

There is little with which to quarrel in Dr Acheson's remarks, except with respect to the allegation concerning the "inference" I made, which resulted in my "committing an error".

I wish to assure him that I, for my part, made no inferences concerning the findings of Coffey and Jessop, nor, for that matter, concerning those of the Iowa and Los Angeles groups. It was my purpose solely to record faithfully, and so direct attention to, seemingly conflicting views as they were reported in the medical literature.

Surely, Dr Acheson does not feel I erred when I questioned the validity of including in the study patients in whom the diagnosis of influenza was established on the basis of the answer they gave to the query, "Have you had influenza during this pregnancy?" Dr Acheson's precise account of just some of the many factors involved in epidemiological investigations would lead one to assume that he himself would be reluctant to sanction such a technique. Consequently, I fail to understand just where I committed the error to which Dr Acheson alludes. Perhaps there were other criteria for diagnosis in the Dublin investigation that were not reported.

The truth of my original statements (Jan 9), composed as they were essentially of excerpts from already documented investigations, cannot be denied, any more than Dr Acheson can deny that the conflict in opinion, as originally reported in the literature, exists. As for his attack on my position in the matter, I simply took no position, having been too thoroughly conditioned by the smoking and cranberry crises to permit myself to draw inferences as to cause and effect relationships. Any implications that are imputed to me must depend for their validity solely on data already reported in the literature.

Paradoxically enough, Dr Acheson in admirable fashion, by delineating so lucidly the complexity of the planning necessary in controlled studies, lends immeasurable strength to my contention that conclusions as to teratogenic effects of disease must be made with the utmost caution. This essentially was the only implication I intended, and pari passu, the only inference that he should have derived from my comments.

Dr Acheson's comments are indeed welcome, as well as informative, because he himself planned the early stages of the Dublin study.

Seaside Memorial Hospital
of Long Beach,
Long Beach, California

GEORGE X TRIMBLE

HYPERBILIRUBINÆMIA IN PREMATURE INFANTS

SIR,—I agree with the summary of Dr Corner and her colleagues that the development of hyperbilirubinæmia in premature infants is directly related to the gestation age. In 1956 I reported[1] 22 cases of hyperbilirubinæmia in the premature, 12 of whom had exchange transfusions; I believe they were the first reported cases of hyperbilirubinæmia in the premature so treated. It was considered that vitamin K was not of ætiological importance in the production of hyperbilirubinæmia in the premature. From the study it was evident that hyperbilirubinæmia in the premature was more likely to occur in the infant of low gestation age, who was œdematous, and feeble at birth; attention was also drawn to the occurrence of hyperbilirubinæmia in the infant of the diabetic mother. Since that time low gestation age and accompanying œdema have been consistently noted in these cases. To date 6 infants of diabetic mothers have had exchange transfusions at the National Maternity Hospital because of hyperbilirubinæmia.

Department of Pædiatrics,
Royal College of Surgeons
in Ireland Medical School,
National Maternity Hospital, Dublin

SHEAMUS DUNDON

DEATHS FROM LUNG CANCER

SIR,—The number of deaths from lung cancer for 1958, published recently, was 19,820, including 17,040 males. The 1948 figures for "respiratory cancer" were 9465 males and 2158 females. It seems that the male-to-female ratio has considerably increased.

If smoking is the cause and if it is accepted that more women are now smoking than used to, one would expect this ratio to decrease instead of increase. What have the statisticians to say?

Sutton, Surrey

S HULME

CRYPTOGENIC LIVER ABSCESS

SIR,—I was very interested to read Dr Stokes' paper of Feb 13. In England the population may normally be presumed to be not "at risk" of amœbic infection, but conditions here are the reverse because amœbic infection is so widespread. It is my impression that in the many liver abscesses seen, the non-amœbic pyogenic abscess is by no means uncommon. The amœbic and non-amœbic varieties of abscess are distinguished by the naked-eye characteristics of the pus, since amœbæ are usually not recovered even from known amœbic abscesses, and cultures have been negative even from clearcut pyogenic abscesses—possibly because of antibiotic treatment given before drainage.

I have operated on 3 such cases during the past five years in which the pus was distinctly white or whitish yellow and therefore left no doubt that the abscesses were non-amœbic. There was no history or other evidence of infection in the area of drainage of the portal vein, and all the patients recovered after drainage and antibiotic treatment. All were "solitary" abscesses, so that a single liver abscess is by no means synonymous with amœbic abscess, as stated in some textbooks.

A healthy Englishman, an athletic outdoor type of 50, developed acute right upper abdominal pain with severe toxæmia and congestion of the right lung base. He had a corresponding leucocytosis. Treatment with emetine, penicillin, and, later, broad-spectrum antibiotics did not bring remission. Drainage through the bed of the 12th rib led to an abscess cavity about 2 in × 2 in. containing white sterile pus. A smear showed only pus cells, no organisms. While convalescing, he had a brisk melæna, which needed a blood-transfusion. Subsequent radiological examination of the gastrointestinal tract, and cholecystographic and urographic studies showed no abnormality. Frequent stool examinations were negative for ova or cysts throughout the illness.

He made a complete recovery, and rejected the advice to leave the country, given on the suspicion that he may have contracted a 'tropical' disease and that stay in the tropics may be prejudicial to his health. He has been well without any trace of recurrence of bowel or other symptoms almost five years after his illness.

This patient suffered from a clearcut acute infection resulting in a pyogenic liver abscess, and a hæmorrhage from the bowel. Could he have had a silent ulcer of the terminal ileum, which led to a metastatic liver abscess, and later hæmorrhage? My colleagues and I have seen a number of cases of solitary ulcers in the terminal ileum which have presented for the first time figures of Perthes' disease in the African, I am, however, quite convinced that it occurs frequently and that as the African advances in civilisation will be seen in hospitals at an earlier stage and more commonly Whether this will be true of all Negro races is quite another matter

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[1] *J Irish med Ass* 1956, 39 99.

Mpilo Hospital, Bulawayo P E S PALMER

AN EASIER ALPHABET

SIR,—May I thank Dr Thomas (May 14) for explaining so clearly the difference between "redundancy" and "noise"? He is entirely correct in saying the patients in the group described (April 23) were unable to exclude noise from signal and had a low signal/noise ratio

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bizarre act in which symptoms are

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Whittingham Hospital,
near Preston

CHROMOSOMES

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3 Ferguson
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5 Bock J A, Fraccaro

the injections being carried out by the medical officer because it is easy for him to assemble the individuals at the local council depot as they finish work. General practitioners, I find, have no objection to such an arrangement.

If the council so decide the cost of the tetanus toxoid may be borne by the council or, alternatively, individuals may be asked to pay the few shillings involved. I have found that more than 90% of the staff agreed to have the injections when they were offered free, but the response may be smaller if payment is involved.

Private firms employing a medical officer no doubt make similar arrangements with their employees but much more could be done on these lines.

The difficulty of a record card remains. As you say in your leading article of May 21, the only sure record would be a tattoo mark, but until the public accept that idea and general agreement is reached on a standardised and quickly recognisable mark some kind of card is the only alternative. A card small enough to fit inside a driving licence has a good chance of being carried by most men most of the time. The details of injections can be recorded on one side and a brief notice printed on the reverse emphasising the importance of telling whoever treats an injury that injections have been given.

Would it be too much to suggest that one of the blank pages of the driving licence might be officially given over to this purpose?

Tangmere, near Chichester. V. P. GEOGHEGAN

MAN AND HIS POSTMORTEM

SIR,—In a debate in the House of Lords on corneal grafting, reported in your issue of May 14, Lord Stonham asked: "Would the noble Lord not suggest to the Minister that *when people come into hospital and are asked to sign an agreement for postmortem*, the words should be added to the form that they are willing, in the event of their decease and providing their relatives have expressed no objection, for their eyes to be used for therapeutic purposes?" Lord St. Oswald replied: "My Lords, I am entirely in sympathy with the noble Lord's aims in regard to this matter, as everyone must be. I will certainly put forward his proposal to the Minister."

The Government's representative in the House of Lords apparently approves of this barbarous way of obtaining permission for postmortem. I suspect that doctors are more humane and kind than their masters but it would be interesting to know whether any hospital still asks the patient's consent for his own postmortem.

Sheffield. JAMES FLINT

NATURALLY OCCURRING ALPHA ACTIVITY OF CIGARETTE TOBACCOS

SIR,—As part of a series of investigations aimed at defining the present levels of natural radioactivity of the human and his environment we have recently measured the alpha activities of a number of cigarette tobaccos. Few data appear to have been published on this subject and those so far reported[1-4] have been concerned either with the beta activity due to potassium 40 or with the radium 226 content of a few specimens of tobacco ash. In the present investigation we have measured the alpha activity due to the naturally occurring radium and thorium series in 51 brands of cigarette and cigar tobaccos from different parts of the world.

Using the alpha-ray counting technique described by us elsewhere,[5] measurements have been made on the ash resulting from the process of smoking the various brands. Each specimen has been measured immediately after ashing, some 4–5 days later, and again after 28 days, by which time the radon 222 lost during combustion would have recovered its equilibrium with the radium 226 present in the ash. Measurements after a further period of a year have been made on many of the specimens. The observed counting rates ranged from 8 to 200 counts per hour, the background of the apparatus being 1 count per hour. The number of alpha counts on which the 28-day measurement of each sample has been based range from 1000 to 3000 and include 50 to 150 observed alpha coincidences from which the activity due to the thorium series has been computed.[5] Table I summarises the results obtained.

TABLE I—ACTIVITIES IN μμC PER 100 G RAW TOBACCO

Type	No. of brands	Mean ash (%)	Total alpha activity			^{226}Ra			^{228}Ra		
			Max	Min	Mean	Max	Min	Mean	Max	Min	Mean
Brazilian cigars	2	20·2	1100	850	975	94	54	74	180	94	137
English cigarettes	31	13·0	279	93	188	32	13	22	36	8	19
American ,,	7	15·6	253	77	162	30	11	21	35	6	16
Italian cheroots	1	23·3	—	—	143	—	—	18	—	—	15
Turkish cigarettes	2	16·5	165	96	131	15	14	14·5	22	7	14·5
Egyptian ,,	1	18·0	—	—	91	—	—	14	—	—	7
American cigars	1	21·5	—	—	90	—	—	18	—	—	4
Russian cigarettes	1	16·0	—	—	81	—	—	13	—	—	6
French ,,	3	18·4	91	50	69	9	7	8·3	11	4	7
Havana ,,	2	19·0	81	40	61	12	3	7·5	7	6	6·5

TABLE II—TOTAL ALPHA ACTIVITIES (μμC PER G)

Brand	% ash	Ash activity	Raw tobacco activity derived from ash measurement	Raw tobacco activity by direct measurement
A	11·9	16·00	1·89	1·90
B	16·9	9·63	1·63	1·87

Measurements of the alpha activity of the raw tobacco were made on two brands selected at random and the values obtained are compared in table II with those deduced from measurement of the ash.

It will be seen from table I that the total alpha activities observed in this series of 51 tobaccos extend over a range of about 30 to 1 with the activities of the various brands showing no apparent correlation with their mineral contents. The range of values of radium 226 is also about 30 to 1 with thorium contents rather more variable and extending over 45 to 1.

Without exception the alpha activities of the specimens of ash increased during the first 28 days after ashing and then remained constant even after a further twelve months. There would appear to be little doubt that most of the equilibrium radon 222 is released during the smoking process and recovers to equilibrium activity during the subsequent 28 days. Bearing in mind the volatile nature of polonium 210 the absence of any further growth of alpha activity of the ash after 28 days points to the fact that lead 210 and polonium 210 are not present in the raw tobaccos at levels of activity of the same order as radium 226.

This is borne out by table II which also indicates that no appreciable fraction of the longlived alpha activity of the tobacco is lost during the smoking process. These findings are in agreement with observations we have made on the smoke and on the distillate. In neither case could we detect the presence of any longlived alpha activity.

It appears from these investigations that the process of smoking cigarette tobacco results in the loss of radon 222 and its shortlived daughters radium A and radium C′. If the equilibrium radon 222 present in the tobacco is lost during combustion and is inhaled with the smoke this would represent a daily intake of 16 μμC of radon in the case of a person smoking 50 per day of the most active brand of English cigarette. If we regard the average radon content of the atmosphere as approxi-

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1 Arregas, F. *C.R. Acad. Sci. Paris* 1938, 206, 1200.
2 Georgescu M. *Bul. Sect. şti. Acad. Române* 1942, 25, 82.
3 Mulvany D. K. *Lancet* 1953, ii, 205.
4 Spiers, F. W., Passey, R. D. *ibid* p. 1259.
5 Turner, R. C., Radley, J. M., Mayneord, W. V. *Brit. J. Radiol.* 1958, 31, 397.

with acute perforation They had been completely "silent" before perforation Could at least some cases of vague bowel upsets seen here not be due to ileal ulceration, which recovers spontaneously? Certainly stools are negative for amœba or amœbic cysts in a large majority of these cases

I feel there is a case for a more critical attitude towards the "tropical liver abscess" which should no longer be presumed to be amœbic—no more than all fevers with rigors should be presumed to be due to malaria

Jinnah Central Hospital,
Karachi
SAID AHMAD

BLINDNESS IN WEST AFRICA

SIR,—I should like to point out a few inaccuracies in the review of my book *Blindness in West Africa* in *The Lancet* of April 30 You state that the methods used are not described This is incorrect Full details are given in the opening parts of chapter IV under the headings

(1) The standard of blindness adopted
(2) The incidence of blindness
(3) Methods of selection of types of project, of places, and of patients
(4) Results (which specify all the places visited, the incidence of blindness in these places, and the causes of blindness by diseases with explanatory notes)

With this information it is difficult to think of any factor missing from the description given as to the method of determining blindness Seldom can a survey of this type have been more fully described

The second misleading statement is that too many places were visited, thereby sacrificing detail and precision For a survey which was intended to assess the *incidence* of blindness, the opposite criticism might more fairly be levelled, but, as I said in my preliminary report, it had been decided to do a little well than a lot badly Ten patients a day on average were examined They could not have been examined more painstakingly This answers your criticism, I hope

A third inaccurate point is your criticism of my reasons for categorising the punctate keratitis as not necessarily due to onchocerciasis because microfilariæ are present, and for attributing the posterior uveitis to onchocerciasis because there is a recognisable onchocerciasis lesion in the anterior segment This is absolutely logical 60% of people, my book says, are infested with onchocerciasis, but only 3% are blind, and perhaps 20% exhibit lesions Thus the presence of living microfilariæ proves little, on the other hand, where there is an onchocercal keratitis, we know there are dead microfilariæ present, and that the subject has no immunity to the disease, therefore, it is quite logical to suppose in the latter case that posterior lesions are due to the same cause as the anterior I go on and show in a later chapter that biopsies of the eye confirmed this view

Your review says the method of assessing the individual density figure is open to criticism because an arbitrary score is given You do not say why I do not believe anyone could say why The method was developed statistically by Mr Alan Brown, of Cambridge University It is unwieldy but not inaccurate

Finally, you state that it is a pity the Southern Cameroons was not included in the study That seems an irrelevant remark in a review of a survey the terrain of which was selected by an advisory medical panel in London, in point of fact, however, a large portion of the Southern Cameroons *was* surveyed

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F C RODGER

*** Concerning the methods of the survey, we had difficulty because there was no attempt to state how random samples were taken from villages or to show that the samples were a representative cross-section Dr Rodger does not say how often selected villages were not subsequently included in the sample nor how the numbers of blind in the villages were ascertained, and these pieces of information seem vital to the determination of the incidence of blindness

Chapter IV states "we did not carry out a survey of the incidence of blindness in every one of the places we visited," and determination of the incidence could certainly go awry if not all the villages were included We still have the impression that a more precise picture would have emerged from a less extensive survey with more rigorous standards

Regarding Dr Rodger's third point, onchocercal keratitis may indicate the presence of dead microfilariæ in the cornea, but there are very good reasons for believing that dead microfilariæ may occur there when there are none in the posterior segment of the eye, and, as he remarks in his book, it is remarkably hard to distinguish between posterior-segment lesions due to onchocerciasis and those due to other conditions

In the matter of the individual density figure, a score admitted to be arbitrary must, by definition, be derived largely from opinion This may be a method of assessing what is considered to be dangerously pathogenic but it does not seem to be an accurate measure of the density of an infection

The southern extremity of the survey, as shown in a map in the book, was on the Cameroons plateau and did not extend into the coastal rain-forest belt with a climate very different from that on the plateau

We should not like these criticisms to obscure the main points of our review—namely, that the book is "the result of painstaking labour" upon which Dr Rodger "is to be congratulated", and that, though many aspects of this subject remain highly controversial, "this book stands out as a lively and helpful contribution to the forum"—ED L

THE PREVENTION OF TETANUS

SIR,—Dr Fulford's paper (May 21) should be read by everyone concerned with the treatment of injuries Antitetanus serum is a potentially dangerous drug and may even cause death Yet it is still being given in casualty departments whose staff are not acquainted with the fact that a second injection is virtually useless to prevent tetanus and is a frequent cause of morbidity, often greater than that due to the injury for which it was given That tetanus can develop even after a first injection of serum makes one suspicious of its real effectiveness

Toxoid immunisation should be the rule for all persons previously exposed or liable to the risk of tetanus, but should the burden be thrown on to the casualty department, whose responsibilities are heavy enough already? In the department under my charge, between 250 and 300 patients a week are candidates for immunisation This means a total of more than 45,000 injections per year to be given by two full-time and one part-time casualty officer and a minimum nursing staff in addition to their normal 24-hour service Shall we be criticised in the coroner's courts if we fail to give toxoid immunisation and a patient dies after a second injury at a later date?

As Dr Fulford points out, the disappearance of National Service is removing the most important source of toxoid immunisation The problem is a national one, deserving the attention of Ministers and medical officers of health and not confined to the paltry efforts of casualty departments, however willing

The Royal Infirmary,
Sheffield
W J W SHARRARD

SIR,—Whilst it is true to say that the surest way to prevent deaths from tetanus is the adoption of a programme of active immunisation of children, there are large numbers of adults whose work exposes them to a risk of tetanus

Local authority staffs engaged on refuse disposal, cesspool emptying, sewerage, building inspection, and other outdoor work particularly in rural areas can be and are being immunised by medical officers of health There are obvious advantages in the injections being carried out by the medical officer because it is easy for him to assemble the individuals at the local council depot as they finish work. General practitioners, I find, have no objection to such an arrangement.

If the council so decide, the cost of the tetanus toxoid may be borne by the council or, alternatively, individuals may be asked to pay the few shillings involved. I have found that more than 90% of the staff agreed to have the injections when they were offered free, but the response may be smaller if payment is involved.

Private firms employing a medical officer no doubt make similar arrangements with their employees but much more could be done on these lines.

The difficulty of a record card remains. As you say in your leading article of May 21, the only sure record would be a tattoo mark, but until the public accept that idea and general agreement is reached on a standardised and quickly recognisable mark some kind of card is the only alternative. A card small enough to fit inside a driving licence has a good chance of being carried by most men most of the time. The details of injections can be recorded on one side and a brief notice printed on the reverse emphasising the importance of telling whoever treats an injury that injections have been given.

Would it be too much to suggest that one of the blank pages of the driving licence might be officially given over to this purpose?

Tangmere, near Chichester **V P GEOGHEGAN**

MAN AND HIS POSTMORTEM

SIR,—In a debate in the House of Lords on corneal grafting, reported in your issue of May 14, Lord Stonham asked " Would the noble Lord not suggest to the Minister that *when people come into hospital and are asked to sign an agreement for postmortem*, the words should be added to the form that they are willing, in the event of their decease and providing their relatives have expressed no objection, for their eyes to be used for therapeutic purposes? " Lord St Oswald replied ' My Lords, I am entirely in sympathy with the noble Lord's aims in regard to this matter, as everyone must be. I will certainly put forward his proposal to the Minister."

The Government's representative in the House of Lords apparently approves of this barbarous way of obtaining permission for postmortem. I suspect that doctors are more humane and kind than their masters, but it would be interesting to know whether any hospital still asks the patient's consent for his own postmortem.

Sheffield. **JAMES FLINT**

NATURALLY OCCURRING ALPHA ACTIVITY OF CIGARETTE TOBACCOS

SIR,—As part of a series of investigations aimed at defining the present levels of natural radioactivity of the human and his environment we have recently measured the alpha activities of a number of cigarette tobaccos. Few data appear to have been published on this subject and those so far reported[1–4] have been concerned either with the beta activity due to potassium 40 or with the radium 226 content of a few specimens of tobacco ash. In the present investigation we have measured the alpha activity due to the naturally occurring radium and thorium series in 51 brands of cigarette and cigar tobaccos from different parts of the world.

Using the alpha-ray counting technique described by us elsewhere,[5] measurements have been made on the ash resulting from the process of smoking the various brands. Each specimen has been measured immediately after ashing, some 4–5 days later, and again after 28 days, by which time the radon 222 lost during combustion would have recovered its equilibrium with the radium 226 present in the ash. Measurements after a further period of a year have been made on many of the specimens. The observed counting rates ranged from 8 to 200 counts per hour, the background of the apparatus being 1 count per hour. The number of alpha counts on which the 28-day measurement of each sample has been based range from 1000 to 3000 and include 50 to 150 observed alpha coincidences from which the activity due to the thorium series has been computed.[5] Table I summarises the results obtained.

TABLE I—ACTIVITIES IN µµC PER 100 G RAW TOBACCO

Type	No of Brands	Mean ash (%)	Total alpha activity			^{226}Ra			^{228}Ra		
			Max	Min	Mean	Max	Min	Mean	Max	Min	Mean
Brazilian cigars	2	20·2	1100	850	975	94	54	74	180	94	137
English cigarettes	31	13·0	270	93	188	32	13	22	36	8	19
American "	7	15·6	253	77	162	39	11	21	35	6	16
Italian cheroots	1	23·3	—	—	145	—	—	18	—	—	15
Turkish cigarettes	2	16·5	165	96	131	15	14	14·5	22	7	14·5
Egyptian "	1	18·0	—	—	91	—	—	14	—	—	7
American cigars	1	21·5	—	—	90	—	—	18	—	—	4
Russian cigarettes	1	16·0	—	—	81	—	—	13	—	—	6
French "	3	18·4	91	50	69	9	7	8·3	11	4	7
Havana "	2	19·0	81	40	61	12	3	7·5	7	6	6·5

TABLE II—TOTAL ALPHA ACTIVITIES (µµC PER G)

Brand	% ash	Ash activity	Raw tobacco activity derived from ash measurement	Raw tobacco activity by direct measurement
A	11·9	16·00	1·89	1·90
B	16·9	9·63	1·63	1·87

Measurements of the alpha activity of the raw tobacco were made on two brands selected at random and the values obtained are compared in table II with those deduced from measurement of the ash.

It will be seen from table I that the total alpha activities observed in this series of 51 tobaccos extend over a range of about 30 to 1 with the activities of the various brands showing no apparent correlation with their mineral contents. The range of values of radium 226 is also about 30 to 1, with thorium contents rather more variable and extending over 45 to 1.

Without exception the alpha activities of the specimens of ash increased during the first 28 days after ashing and then remained constant even after a further twelve months. There would appear to be little doubt that most of the equilibrium radon 222 is released during the smoking process and recovers to equilibrium activity during the subsequent 28 days. Bearing in mind the volatile nature of polonium 210 the absence of any further growth of alpha activity of the ash after 28 days points to the fact that lead 210 and polonium 210 are not present in the raw tobaccos at levels of activity of the same order as radium 226.

This is borne out by table II which also indicates that no appreciable fraction of the longlived alpha activity of the tobacco is lost during the smoking process. These findings are in agreement with observations we have made on the smoke and on the distillate. In neither case could we detect the presence of any longlived alpha activity.

It appears from these investigations that the process of smoking cigarette tobacco results in the loss of radon 222 and its shortlived daughters radium A and radium C'. If the equilibrium radon 222 present in the tobacco is lost during combustion and is inhaled with the smoke this would represent a daily intake of 16 µµC of radon in the case of a person smoking 50 per day of the most active brand of English cigarette. If we regard the average radon content of the atmosphere as approxi-

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1 Arrigas F C.R. Acad Sci Paris 1938, 206, 1200.
2 Georgescu M Bull Sect sci Acad Roumaine, 1942 25 82.
3 Mulvany D K Lancet 1953, ii 205.
4 Spiers F W Passey, R D ibid p 1259.
5 Turner R C, Radley, J M, Mayneord W V Brit J Radiol 1958, 31, 397.

mately 0 1 $\mu\mu$C per litre and the mean air exchange rate as 20,000 litres per person per 24 hours, then the average daily intake of radon 222 by the general population is approximately 2000 $\mu\mu$C

It seems therefore that even in the case of the heavy smoker the additional alpha activity taken into the lungs per day due to the radium content of the cigarettes themselves, is less than 1% of the atmospheric radon inhaled per day by both smoker and non-smoker

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R C TURNER
J M RADLEY

MOSAICISM IN KLINEFELTER'S SYNDROME

SIR,—Ford and his colleagues [1] reported a patient with Klinefelter's syndrome in whom they had discovered a presumptive XXY/XX mosaic of the sex chromosomes We are now making a preliminary report of a patient with an apparently identical sex chromosome constitution

Our patient, a man aged 37 years, is a psychopath He has no facial hair, the axillary hair is scanty, and the pubic hair is sparse and of feminine distribution He has no gynæcomastia His testes are small and soft but no testicular biopsy has been performed The hormonal urinary metabolites are 17-ketosteroids 2 mg per 24 hours, 17-hydroxy-corticosteroids 13 mg per 24 hours (Norymberski method), gonadotrophins approximately 200 HMG 24 per 24 hours, which is in the normal range for postmenopausal women A presumptive diagnosis of Klinefelter's syndrome was made and this was confirmed by a buccal mucosal smear which showed that the majority of the nuclei were chromatin-positive Out of 250 such positive cells 83% had a single chromatin particle but the remainder showed two such particles

A bone-marrow examination was made by a modification of the method of Ford et al [2] 100 undamaged cells were examined for chromosomal content and 45 of the cells had 46 chromosomes and 55 of the cells had 47 chromosomes 33 of these cells were analysed in detail, and 13 cells had 46 chromosomes, all of which were found to be of normal female karyotype, and the remaining 20 cells had 47 chromosomes and were XXY in constitution, the autosomes being of a standard type This patient then has the same presumptive chromosomal pattern of XXY/XX as did the patient with Klinefelter's syndrome reported by Ford et al

A fuller report of this patient will be published in *Heredity* in which the problems of sex chromosome mosaicism [3] will be critically considered

This work was done in conjunction with the department of genetics (Prof K Mather) and the department of pædiatrics and child health (Prof Douglas Hubble), and one of us (M D H) is a research scholar supported by the United Birmingham Hospitals Endowment Research Fund

Department of Clinical Endocrinology,
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A C CROOKE

Department of Genetics in association with
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University of Birmingham

M D HAYWARD

SURGERY OF THE ŒSOPHAGUS

SIR HENEAGE OGILVIE writes

"In my Grey Turner lecture [4] I mentioned that the first surgeon to resect the œsophagus was Czerny *Unfortunately* I find that the portrait (fig 448) is that of Prof Adalbert Czerny of Berlin, while the surgeon *who first resected the œsophagus* was Prof Vinzenz Czerny of Heidelberg My informant is *Prof F Stelzner of Hamburg, who sends a photograph of* Professor Czerny of Heidelberg Unfortunately all that I can do now is to apologise for the error"

Obituary

ROBERT McCARRISON

Kt, C I E, M A Oxon, M D R U I, D Sc, L L D Belf, F R C P

Major-General Sir Robert McCarrison, who died on May 18 in Oxford at the age of 82, spent much of his life in India where, he used to say, "nature makes large-scale experiments on man" By his intelligent observation of these experiments and by his own controlled investigations he made outstanding contributions to nutrition and to preventive medicine

He came from an old Irish family and after graduating M B at Belfast in 1900 he entered the Indian Medical Service At his first station he met an apparently new disease, the "three-day fever of Chitral" After careful observation he became convinced it was transmitted by the sand-fly (*Phlebotomus*) and sent for a microscope, but he was posted elsewhere before obtaining proof Five years later his hypothesis was confirmed by Doerr (1908) At this early time McCarrison began to study goitre and cretinism, and was *at once* impressed by the effects of deficient food *on the thyroid* gland, and he began a general investigation *of the nature* of deficiency diseases This work was interrupted in 1914 by four years' active service

J Russell and Sons

On his return in 1918 he acquired an empty *room in the* Pasteur Institute at Coonoor, he borrowed a table for his own microscope and *Cambridge* rocker microtome, borrowed his wife's cook to cut sections and a clerk from the post-office *When four months later his* magnificent *Sikh* assistant, Mula Singh, returned from the war the cook was released for normal duties *In 1920 McCarrison* was invalided to *England* for a year He paid for Mula Singh to accompany him for further training in *histology* in Oxford, while he *himself* worked in Sherrington's laboratory on the relation of dietary fat to the thyroid gland

On McCarrison's return to India in 1922 his apparatus had been dispersed, but he managed to get back the empty room until his work was stopped the following year on grounds of economy He resigned In 1925 he returned to the empty room with his assistants Mula Singh and Krishnan, and by battling with obtuse officials he acquired and trained assistants When in *1926 Lord* Linlithgow visited India as chairman of the Royal Commission on Agriculture *he* was impressed by a memorandum written by McCarrison, though his advisers and officials tried to dissuade him, the future Viceroy insisted on visiting Coonoor to see the allegedly trivial work being done there and the Commission recognised its importance and promise Indeed, after hearing *McCarrison's* exposition, the Rajah of Parlakimedi, who was one of the members, immediately *presented a lakh of rupees* to the research unit In 1929 the Commission made this unit into Nutrition Research Laboratories with McCarrison as the director, and for the first time in his life he had adequate facilities which he steadily improved until he retired from India in 1935

On their return from India McCarrison and his wife settled in Oxford where they kept open house During the late war he was chairman of the local medical war committee and deputy regional adviser in medicine to the E M S From 1945 until 1955 he was

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1 Ford, C E, Polani P E, Briggs, J H, Bishop, P M F *Nature, Lond* 1959 183, 1030
2 Ford C E, Jacobs P A Lajtha L G *ibid* 1958 181, p 1565
3 Court Brown W M Jacobs, P A, Doll R *Lancet*, Jan 16 1960, p 160
4 *Brit J Surg* 1960, 47 457

director of Postgraduate Medical Education in the university and he served on various committees He had given the Milroy lectures at the Royal College of Physicians in 1913, and on his return from India he gave the Cantor lectures at the Royal Society of Arts (1936), the Lloyd Roberts lecture (1936), the Gabriele Howard lecture (1937), and the Sanderson-Wells lecture (1939) His honours were many, and included the first class of the Kaisar-i-Hind gold medal (1911), and the Prix Amussat of the Paris Academy of Medicine (1914) He was appointed C.I E in 1923 and knighted in 1933

At the request mainly of Indian scientists, McCarrison's more important papers were edited by Dr H M Sinclair and presented to him as a *Festschrift* on his 75th birthday At the presentation nothing pleased him more than a telegram from the Minister of Health of India expressing appreciation of his services to the health and well-being of the peoples of that country and of other countries for generations to come

H M S recalls how McCarrison's work combined careful observation in the field with experimental studies on man and lower animals under controlled conditions

"When he was in Gilgit from 1904 to 1911 he studied the endemic goitre in the foothills of the Himalayas He noticed that in eight of the nine villages goitre, cretinism, and idiocy were common, but the ninth village was spared its water came from a pure mountain spring McCarrison and his volunteers thereupon drank twice daily 6 oz of the suspended matter in the grossly polluted water of the eight villages and some developed goitres He determined the iodine content of the water and found it to be sufficient for normal conditions of diet. This early study of goitrogens, resumed by him later, was before the work of Marine on water pollution and goitre in trout (1909), and long before Chesney on cabbage (1928), Purves on rape-seed, and Astwood on thiouracil.

"At the time of his early work little nutritional research had been done in India, though McCarrison was impressed with the work of McCay (1912) on the importance of protein At this time Hopkins, McCollum, and others were studying purified diets on lower animals, mainly rats, and elucidating the specific individual factors needed for health McCarrison deliberately chose a different approach since he realised (as few others did) that single deficiencies were unlikely to occur in man, and that combined deficiencies might produce pathological changes and hence ill health without the production of a specific deficiency disease 'My own method, on the other hand, has been to observe the more general symptomatic and pathological effects of faulty food on the animal body as a whole, and thereby to ascertain what forms of human illness might reasonably be attributed to it' There followed a series of papers on the pathogenesis of deficiency disease, with particular studies of hypertrophy of the adrenals, of beriberi, of urinary lithiasis, and of the general effects of faulty diets in man and lower animals"

In a further tribute R P writes

"In 1901 Robert McCarrison sailed for India and almost immediately found himself in medical charge of an isolated group of soldiers in the Hindu Kush mountains There he began a study of the goitre endemic in the natives and so began his scientific career For those whose duties it is to plan modern curricula for medical students, it may be a useful thought that at the age of 23, when few modern students are registered, McCarrison held a responsible post in a remote part of the world far away from any medical or scientific help By present standards his formal education was hopelessly inadequate Yet at this early age he had the priceless opportunity to use his imagination and creative energies Singlehanded and against continual opposition from the financial authorities of the time, he laid the foundations for scientific nutrition work in India When he retired from India he left a flourishing laboratory at Coonor with a small staff of enthusiastic Indians There was a tradition of careful and accurate laboratory work on experimental animals, and his vivid imagination had pointed the way to many practical problems affecting the health of the peoples of India Many nutritionists, a few British but mostly Indian, who have never been personally associated with Sir Robert, are yet conscious of a great debt to him For he left behind him buildings, an organisation, and, perhaps most important, a climate of opinion, which others have been able to develop, so that his laboratory, now moved to Hyderabad, has become one of the leading nutritional institutes in the world

"Sir Robert both in his writings and in his lectures was passionately concerned with the need to relieve the misery of so many poor Indians, caused by poverty and inadequate diets He often pointed out that the traditional diets of many parts of India were excellent, but the people were too poor to get the foods to which their forefathers had been accustomed Scientific knowledge could lead to a fresh union between a flourishing agriculture and health Knowledge gained by McCarrison and his school has already contributed significantly to the welfare of innumerable Indians—but certainly not on the scale that he would have wished and which he always maintained was practical He was one of the small band of research-workers in the Indian Medical Service who revolutionised the health of the country His work on nutrition ranks with that of Ross, Christophers, and Sinton on malaria, of Rogers on cholera, and of Megaw on typhus He was a great fighter for, and true servant of, the Indian people."

Sir Robert married in 1906 Helen Stella, daughter of J L Johnston, I C S, and she survives him

LEONARD FOSTER BROWNE

M D Durh.

Leonard Browne, who died on May 15, was an early member of the staff of the Tavistock Clinic He was also a former vice-chairman of the London County Council

He was born in 1887 in Sunderland and he was educated at Sedbergh School and the University of Durham After qualifying in 1909, he served as house-physician at the Royal Victoria Infirmary in Newcastle upon Tyne He took the M D with gold medal in 1913 Before the 1914–18 war he worked at the Christian Missionary Hospital at Cairo, and during the war he served in France and Flanders in the R A M C He was one of the founders of Toc H and was the first treasurer He preserved a close contact with this movement for the rest of his life, serving as a trustee since 1947

In the early years after the war, Browne, with a few others, saw a new means of combining religious and medical loyalties in the "new psychology" He joined the staff of the Tavistock Clinic under Hugh Crichton-Miller, and its activities remained one of his life-long concerns Of his work in this new specialty J D S writes

"Browne enjoyed great popularity as a lecturer because of the pithy way in which he presented his subject matter, his manifest common sense, and his pawky humour At this time too he was greatly in demand in his private practice as a psychotherapist Though he did not publish much, the contribution he made to the growth of the new subject of psychotherapy was valuable Toleration and a sound practical sense were not always prominent amongst the early enthusiasts for this newcomer to medicine, and the quick way in which Browne made his sterling qualities felt must have reassured many sceptics in those early days A story he told of his sometimes unorthodox treatment in his early days, when therapeutic principles were less systematised, gives a vivid impression of his spontaneity He had a [illegible] silent patient and was beginning to feel at a loss what to try next to try to break through the resistance Browne then leaned forward and placed a penny beside the surprised patient who inquired what this was for Browne answered, almost certainly with a characteristic twinkle, 'Your thoughts'"

When the late war began, Browne volunt

military service He became psychiatrist to the Eastern Command and London District, and was promoted to the rank of lieut -colonel in 1943 In these posts he gave valuable help with young soldier battalion, and personnel selection, and as a general adviser on aspects of morale After the war, when their Army experience led the staff of the Tavistock Clinic to evolve a new policy which created the Tavistock Institute of Human Relations, Browne, now too old to serve on the staff, became a member of the council of the new body and for several years was its vice-chairman

Outside his profession he served others through his work for local government He was elected to the London County Council in 1946, and in 1949 he became a county alderman He served on the children's committee for some years, but perhaps his greatest work was done on the education committee He was chairman of the special education subcommittee, and during his term of office six additional boarding-schools for maladjusted children and three for educationally subnormal children were opened He also took an active interest in the child psychiatric services and in the extension of the child-guidance services He was vice-chairman of the Council during 1957–58

Dr Browne married in 1923 Violet, daughter of the late Rev Richard Bott, and they had two daughters and a son A memorial service was held in All Hallows-by-the-Tower on May 21, which was taken by the Rev P B Clayton, M C, the original Toc H chaplain

DR HINDS HOWELL

A S MacN writes

"Conrad Meredyth Hinds Howell was a cultured, learned, and able physician Trained in the Oxford school of physiology, whose foundations were so well and truly laid by Burdon Sanderson and Francis Gotch, he was early interested in neurology at a time when new knowledge of the central nervous system based on experimental research in physiology was being applied to the diagnosis and treatment of nervous diseases Primarily a general physician—he was the author (with H W Wilson) of a treatise on *Movable Kidney*—after his appointment as assistant physician to The National Hospital, Queen Square, his reputation as a neurologist increased, and, eventually, he established the neurological department at St Bartholomew's Hospital But he told me that he still saw patients with other forms of disease and held, as did Victor Horsley, that a man was the better neurologist if he maintained his acquaintance with general medicine"

Parliament

Consultants Criticised

On the adjournment on May 19 Mr W Griffiths drew attention to two criticisms of consultants in the National Health Service that there was a short cut to the hospital ward via a consultant's private room, and that a patient referred to an outpatient department often did not see the consultant to whom he was sent but a registrar Mr Griffiths supported his case by letters from patients and general practitioners What, he asked, was the trouble? Had we too few consultants, or did those that we had give preference to private fee-payers in the outpatient departments? Or was it just that consultants did not turn up on time at the clinics? Was this inherent in the part-time system? Was it really impossible to try to run the economics of private enterprise hand-in-hand with a public, full-time service? He suggested that at the clinics the patients should at the very least be told who was seeing them Why not have an occasional spot check on selected wards to verify how the people in its beds on that day were admitted? What about a check on simple surgical cases, such as hernia or varicose veins, admitted last year to one hospital, and a comparison of the waiting-time of those admitted after private consultation with that of people who went through the normal channels of the outpatient department?

Dr Edith Summerskill said that rumblings of discontent from registrars had reached her Many felt frustrated because they had not reached consultant status It had been impossible to promote them to that status because there were not sufficient vacancies They felt that they were called too often to deputise for the consultants There had also been complaints that young men and women who were doing preregistration jobs had been asked to do too much of the work which should fall to the registrars

Miss Edith Pitt, parliamentary secretary to the Ministry of Health, said that the cases Mr Griffiths had raised concerned a hospital under the Board of Governors of the United Manchester Hospitals The Board had assured her that patients recommended for admission to hospital after a private consultation who did not wish to go into a pay-bed were put on the ordinary waiting-list and were subject to the same considerations regarding urgency as other patients Detailed information about comparative periods of waiting would involve the examination of thousands of individual case-records She had taken note of the suggestion of a spot check Turning to the second question, she said that there was nothing essentially wrong in the present system of clinical organisation which, incidentally, provided the means by which registrars gained practical experience It was an accepted part of hospital staffing arrangements, but the delegation was done expressly by the consultant, who retained his ultimate responsibility for the patient

Mentally Handicapped Children

On the adjournment on May 18 Mr Compton Carr drew attention to the needs of children who are ineducable in normal schools and who therefore fall under the care of the health rather than the education authorities Too many of these children were unable to find places in the occupation and training centres which for them should take the place of schools The supervisors of these centres were ill paid and usually had only one year's training He thought that their salary scale should be revised and that a national training scheme should be introduced

Miss Edith Pitt, parliamentary secretary to the Minister of Health, said that local health authorities had been making great efforts to provide more places for mentally handicapped children In 1948 there were about 100 centres catering for about 4000 children At the end of 1959 there were 314 catering for 10,500 children In the financial year 1960–61 authorities had submitted 69 schemes for training-centres for juniors or juniors and adults mixed When the Minister asked all local health authorities a year ago to review their mental health services in the light of the report of the Royal Commission on Mental Health, he suggested that they should keep in the forefront the need for adequate provision for training children up to the age of sixteen and should consider the desirability of providing residential accommodation in hostels for children who could not reasonably be transported to a training-centre every day Hostels of this kind would go a long way to provide places for the 2600 children who at the moment were not being trained Many of them lived at distances from the centres which made it difficult, and against the interests of the child, to convey the child every day to and from the centre The children would be able either to stay in the hostels for the whole term or to return home at weekends Earlier this year the Standing Mental Health Advisory Committee had set up a subcommittee on the training of staff of centres for the mentally subnormal It was now receiving evidence and had issued a questionnaire to local health authorities and hospitals She hoped that the results of the committee's deliberations would help the Ministry to provide more and better staffs for training centres

Transistor Hearing-aids

Initial supplies of transistor hearing-aids have been dispatched to hearing-aid distribution centres to enable a start to be made on the issue of these aids to adults It will take a considerable time to replace valve aids by transistor aids, and the Minister of Health has suggested to hospital authorities that, subject to the otologist's discretion to prescribe a 'Medresco' transistor aid for a particular patient where he thinks it clinically necessary, and after the prior claims of children and war-pensioners have been met, the order of priorities for issuing these aids to adults should be as follows

(1) Adults who received a transistor aid as children and require a replacement.

(2) The deaf-blind

(3) Those who are dependent on a hearing-aid for employment and are severely handicapped in their work by a valve aid.

(4) Mothers with young children, and those who because of physical disability cannot make full use of a valve aid.

Diary of the Week

MAY 29 TO JUNE 4

Monday, 30th

UNIVERSITY OF LONDON
5 P.M (University College Hospital Medical School, University Street, W C.1) Prof M K. Krishna Menon (Madras) Evolution of the Curative Treatment of Eclampsia.

UNIVERSITY COLLEGE, Gower Street, W C.1
5 30 P.M Sir Aubrey Lewis Agents of Cultural Advance. (Hobhouse lecture)

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
5.30 P.M *Library (Scientific Research)* Mr H R. Verry Document Copying and Office Printing Processes

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W 12
4 P.M. Prof John Crofton The Problem of Tuberculosis

Tuesday, 31st

ST MARY'S HOSPITAL MEDICAL SCHOOL Paddington W.2
5 P.M. Dr Mavis Gunther Physiology and Management of Human Lactation.

INSTITUTE OF DERMATOLOGY, Lisle Street, W C.2
5.30 P.M. Dr P E Bodkin Applied Physics

Wednesday, 1st

ROYAL SOCIETY OF MEDICINE
5 15 P.M *History of Medicine* Mr James Kemble Napoleon—A Man Condemned to Live.
8 P.M. *Surgery* Dr Frank Adair (New York), Prof D W Smithers, Mr J B Hedley Atkins Carcinoma of the Breast.

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr D W Henderson Experiments on Primary and Secondary Respiratory Infection.

ROYAL FREE HOSPITAL, Gray's Inn Road, W C.1
4 P.M Prof P A Bastenie (Brussels) Significance of the Glucose Tolerance Test

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr N H Witten Use of Ionising Radiation in Dermatology

INSTITUTE OF DISEASES OF THE CHEST, Brompton S W 3
5 P.M. Dr R. V Gibson Atrial and Ventricular Septal Defects

UNIVERSITY OF OXFORD
5 P.M. (Radcliffe Infirmary, Oxford.) Prof G L. Montgomery Observations on the Pathology of the Myocardium (Litchfield lecture)

MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8.30 P.M (18 Nicolson Street) Mr R. Leslie Stewart Management and Treatment of the Vesical Papilloma.

Thursday, 2nd

UNIVERSITY OF LONDON
5.30 P.M (Guy's Hospital Medical School, St Thomas Street, S E 1) Prof C. Liebecq (Liège) Biochemical Aspects of Glucose Utilisation in Muscle Tissue.

UNIVERSITY COLLEGE
5 P.M. Dr S J Bach Metabolic Fate of Protein-Nitrogen in the Mammal (Second of two lectures)

ROYAL SOCIETY OF MEDICINE
5 P.M *United Services* Surgeon Captain J L. S Coulter Development of Naval Medical Administration during the 18th Century

POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M Dr J M French Adult Cœliac Disease and Allied Disorders

HONYMAN GILLESPIE LECTURE
5 P.M (University New Buildings Teviot Place Edinburgh) Prof M F A Woodruff New Approaches to the Treatment of Cancer

Friday, 3rd

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M Mr Denis Browne Spina Bifida

UNIVERSITY OF ABERDEEN
5 P.M. (Medical School Foresterhill) Mr J H Johnston Burns

Notes and News

APPROVAL OF DOCTORS FOR MENTAL HEALTH ACT

UNDER the new Mental Health Act, two doctors must recommend the compulsory admission of a patient to hospital or reception into guardianship One of these must be approved by a local health authority as having special experience in the diagnosis of mental disorder Before approving doctors for this duty the authority must consult at least two members of a professional advisory panel The Minister of Health has now made regulations for the introduction of this new procedure (S I 1960, no 771)

The advisory panel for each area is to be appointed by the regional hospital boards concerned after consultation with the boards of governors of teaching hospitals where appropriate Appointments to these panels will be made on an annual basis and will be renewable Each panel should have at least 4 members, who would collectively have experience of both mental illness and subnormality The Minister of Health has asked that the first appointments to the panels should be made not later than June 11 (H.M 60 35)

The Minister is anxious that an adequate number of doctors distributed conveniently over the country should be "approved" by the panels He suggests that there should be at least one in each hospital which is going to receive detained patients (circular 7/60) The Minister does not wish to suggest any definition of what constitutes "special experience" in the diagnosis or treatment of mental disorder, but he would usually expect doctors with the D P.M or an equivalent qualification, medical officers of local health and education authorities, and general practitioners with a special practical knowledge of mental disorder to be eligible Approval should not be refused because a doctor's special experience does not cover the full range of mental disorder In practice doctors would probably wish not to give recommendations for patients of a category with which they were not normally concerned, but this could not be made a formal condition of approval Approval will normally be given to doctors for periods of five years, after which the panel must review their recommendation The Minister asks authorities to ensure that an adequate number of doctors are approved by September 15

COMPARATIVE BIOCHEMISTRY AND PHYSIOLOGY

A NEW journal of which the first issue has just appeared[1] will include original papers on animal biochemistry and physiology particularly in their comparative aspects In the first issue Barker Jorgensen and his colleagues in the Institute of Comparative Anatomy of the University of Copenhagen discuss the effect on the pars distalis of the pituitary, in toads, of extirpating the median eminence of the hypothalamus Since function was resumed in these animals, Jorgensen et al suggest that the substances activating the pars distalis, which are normally liberated in the median eminence, are produced in other hypothalamic centres as a neurosecretion

University of London

Dr Israel Doniach, reader in morbid anatomy at the Postgraduate Medical School of London, has been appointed to the chair of morbid anatomy at the London Hospital Medical College.

Dr Doniach graduated M B from University College Hospital in 1934 He spent six months as honorary assistant in clinical pathology at U C H till in 1935 he became assistant pathologist at St Mary's Hospital In 1937 he was appointed clinical pathologist and assistant in cancer research at Mount Vernon Hospital, and from 1939 to 1942 he was assistant pathologist in the Emergency Medical Service at that hospital In 1943 he joined the department of morbid anatomy at the Postgradaute Medical School of London as senior assistant in pathology In 1948 he was appointed senior lecturer and in 1950 reader in the department His published work includes papers on changes in meningeal vessels in tuberculous meningitis, uræmic œdema of the lungs, renal complications of pregnancy, histology of gastric and upper intestinal biopsies, tumour production in rats' thyroid with radioactive iodine, and studies in goitrogenesis and thyroid regeneration

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[1] *Comparative Biochemistry and Physiology* January, 1960 Editors Dr G Kerkut, Department of Physiology and Biochemistry University of Southampton and Prof B T Scheer Department of Biology, University of Oregon Eugene Oregon U S A Published by Pergamon Press, 4 Fitzroy Square London, W 1 8 issues a year Annual subscription libraries and other establishments £14, individuals £5 5s

At recent examinations for the D P M M M F Dixon and W R Little were successful

University of Cambridge

On May 14 the degree of M B was conferred on C L C Arnold

University of Sheffield

The following appointments have been made

Dr R B Bradshaw and Dr John Bullock, demonstrators in anatomy, Dr W I H Shedden, assistant lecturer in bacteriology, Dr R L Hunt, part-time clinical teacher in obstetrics and gynæcology, Dr Anne E Walker, Boots medical research fellowship

University of St. Andrews

Dr J T Hemingway has been appointed lecturer in physiology in Queen's College, Dundee.

University of Aberdeen

Dr Grace C Turner has been appointed a lecturer in bacteriology

University of Dublin

On May 19 the following degrees were conferred

M D—P G S Beckett
M Ch—R B Brenan
M B, B Ch, B A O—A A Barclay, David Crookenden, P J Reid, Stanley Steinberg

Royal College of Physicians of London

Dr J G Scadding will give the Mitchell lecture on Tuesday, June 21, at 5 P M, at the college, Pall Mall East, S W 1 He will speak on *Mycobacterium tuberculosis* in the ætiology of sarcoidosis

Royal Faculty of Physicians and Surgeons of Glasgow

On June 1, at 12 30 P M, the honorary fellowship of the faculty will be presented to Princess Alexandra of Kent The Princess will dine with the fellows in the evening

Royal Society of Medicine

The following have been elected to honorary fellowship

Dr F E Adair (New York), Prof Marc Amsler (Zurich), Dr H LeRoy Bockus (Philadelphia), Dame Harriette Chick, Sir William Kelsey Fry, Sir Eardley Holland, Prof Fritz Linder (Berlin), Dr R F Loeb (New York), Sir Philip Manson-Bahr, Prof J H Means (Boston), Sir Clement Price Thomas

Saint Vincent International Prize for Medical Science

This prize, which is worth 10 million lire (about £6000), is offered by the Medical Academy of Turin for contributions to the development of medical science It can be awarded to a single research-worker or to a group collaborating in the same field for work published since 1955 The closing date for nominations is Oct 31 Further particulars may be had from Prof G Baldini, 39, Belgrave Square, London, S W 1

British Association for the Advancement of Science

The annual meeting of this Association will be held in Cardiff from Aug 31 to Sept 7 The president will be Sir George Thomson Further particulars may be had from the secretary, 18, Adam Street, London, W C 2

Sir Arthur Sims Commonwealth Travelling Professorships

Mr Hedley Atkins, Prof T Cecil Gray, and Dr Paul Wood have been appointed to professorships for 1961 Mr Atkins and Professor Gray are to travel in Australia and New Zealand, and Dr Wood will make a tour of Canada

Faculty of Ophthalmologists

The following officers have been elected for 1960–61

President, Mr E G Mackie, vice-presidents, Mr J E M Ayoub, Mr G W Black, hon treasurer, Mr G T Willoughby Cashell, hon secretary, Mr J R Hudson

"Clinical Science"

By an agreement between the Medical Research Society and the Biochemical Society, *Clinical Science* is to be produced by them jointly The intention is "to maintain existing interests, and also to attract an increased proportion of papers of a metabolic or biochemical character in the clinical field" The reconstituted journal will have six issues in the year, the first to appear next February Contributions should go to the chairman of the editorial board, Prof G M Bull, Institute of Clinical Science, Grosvenor Road, Belfast, Northern Ireland

Medical Film Festival

A medical film festival will be held in London on July 5, 6, and 7 under the auspices of the *British Journal of Clinical Practice* (171, New Bond Street, London, W 1)

A Berlin Occasion

The celebration of the 250th anniversary of the Charite will be held in Berlin from Nov 6 to 19, in connection with the 750th anniversary of the Humboldt University Further particulars may be had from Dr Dagobert Muller, Berlin N 4, Schumannstrasse 20–21

Control of Drugs

Representatives of branches of the Pharmaceutical Society decided on May 19, at their annual meeting in London, that the society should press for legislation to ensure that no new substance introduced for medical treatment should be supplied to the public, except on a doctor's prescription, until sufficient evidence is available to justify release from such control

International Congress on Mental Health

This congress will be held in Paris from Aug 30 to Sept 5, 1961 Further particulars may be had from the World Federation for Mental Health, 162, East 78th Street, New York, 21, N Y, U S A, or Ligue Française d'Hygiène Mentale, 11, rue Tronchet, Paris, VIII^{e}

Institute of Cardiology, London

On Friday, June 17, at 5 P M, at 1, Wimpole Street, W 1, Sir Russell Brock will give the St Cyres lecture He will speak on the surgical treatment of pulmonary stenosis

Scottish Hospital Endowments Research Trust

During 1957–59 the Trust approved grants of £106,000 Two new projects which received support are an investigation into causes and management of accidents which reach the Edinburgh hospitals and a study in the South-Eastern Region of patients after their discharge from mental hospitals

Victor Horsley Lecture

Prof N M Dott will give this lecture on Friday, June 24, at 11 A M at B M A House, Tavistock Square, London, W C 1 His subject will be Brain, Movement, and Time

The William Temple Association is holding a series of meetings on law and morals They will include a lecture on suicide by the Rev G R Dunstan, clerical secretary of the Moral Welfare Council, on May 31, and a lecture on penology by Mr A W Peterson, deputy chairman, Prison Commission, on June 14 Both meetings will be at 8 P M, at Liddon House, 24, South Audley Street, London, W 1

Professor Leonhard, of Humboldt University, Berlin, will give a lecture on the treatment of ideohypochondriac and sensohypochondriac neuroses at the Marlborough Day Hospital, 38, Marlborough Place, St John's Wood, N W 8, on Monday, June 20, at 8 15 P M

Colonel F H Blackburn has been elected president of the Territorial Army Medical Officers' Association in place of Brigadier W R Ward, who has retired

A semipermanent exhibition by Dr K V Sanderson on the architecture of basal-cell carcinoma will be held at the Institute of Dermatology, Lisle Street, London, W C 2, from June 1 to 30

CORRIGENDUM *Diagnostic Enzymology*—In this article last week the new sentence in the fourth line under the heading "other serum enzymes" (p 1125) should have opened "Aldolase is *increased* in progressive muscular dystrophy "

The Lancet · Saturday 4 June 1960

"POSTERIOR-COMMUNICATING" ANEURYSMS

A Controlled Trial of the Conservative and Surgical Treatment of Ruptured Aneurysms of the Internal Carotid Artery at or near the point of origin of the Posterior Communicating Artery

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NEUROLOGICAL SURGEON

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M.B Lond, F.R.C S
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DEPARTMENT OF NEUROSURGERY, ST GEORGE'S HOSPITAL, LONDON, S W 1

IN this report we give the first positive results from a clinical trial of surgical and conservative treatment of ruptured intracranial aneurysms The methods were described previously by McKissock, Paine, and Walsh (1958), who said

> "At the present time there is no conclusive evidence indicating the natural death-rate in a large series of unselected cases of ruptured intracranial aneurysms and so there can be no proof of the value of surgical treatment in this condition"

Preliminary review of the figures for our own large series of patients suggests that the untreated cases fared as well as those operated on, which is the conclusion reached by Benson (1958) We thus decided that the truth of this controversial matter could only be revealed by a carefully planned trial After consultation with neurologists unassociated with our unit, and with a statistician, we formulated such a scheme and put it into operation on Jan 1, 1958

The Scheme

Selection of Patients

Inclusion of patients in the trial depended upon criteria established by a routine system of investigation of all cases with bleeding into the subarachnoid space, as follows

1 A general physical and neurological examination was made immediately after admission to hospital

2 If the presence of blood in the subarachnoid space had not been confirmed by the admitting hospital, a lumbar puncture was performed at once to establish this fact

3 Each common carotid artery in the neck was compressed for ten minutes Failure to withstand compression on either side was regarded as contraindicating immediate angiography If the patient failed to withstand compression on one side only we thought it permissible to perform angiography immediately on the side tolerating compression. Usually compression was tolerated after repeated attempts on subsequent days, and appropriate angiography was then undertaken. In patients who still failed to withstand compression of one carotid artery several days after the ictus, angiography was still performed because the risks of this procedure were regarded as less than those of possible further bleeding from the lesion

4 Subject to these contraindications bilateral carotid angiography was undertaken, and, if this was negative, vertebral angiography was done two days later

5 Those patients in whom the causal aneurysm was revealed were, at this point, referred to the neurosurgeon on duty for him to decide whether the aneurysm was operable and whether the patient was suitable for inclusion in the trial The question of operability rested entirely on the surgeon concerned, but whether the patient was included in the trial depended on previously agreed criteria

All patients with proven subarachnoid hæmorrhage in whom a surgically treatable aneurysm had been demonstrated were included in the trial, with the following exceptions

1 Those who died before the necessary investigations could be completed but in whom an aneurysm was found post mortem.

2 Those with multiple aneurysms without evidence as to which lesion had bled, and in whom the aneurysms demonstrated could not be treated by a single operation.

3 Those with angiographic evidence of a large associated intracerebral hæmatoma which appeared to be threatening life, because it was not deemed justifiable to withhold surgery

4. Those in a state of akinetic mutism (which we regard as irreversible) in whom no benefit could be expected from surgical treatment

5 Those with aneurysms regarded as either inaccessible or untreatable by existing surgical techniques

All such patients were *excluded* from the trial, and therefore they are not discussed later in this paper They are *not* included in the series of patients treated conservatively

Technique of Random Selection

Suitable patients were included in the trial series regardless of the gravity of their clinical state, and the treatment to be adopted was then determined.

On the advice of our statistician the cases were grouped according to (*a*) the site of the aneurysm, (*b*) whether the blood-pressure was normal or high, and (*c*) whether they were above or below fifty years of age. They were then subdivided into the two categories previously described by McKissock and Walsh (1956)

Category A—Patients who were likely to die in the immediate future from the hæmorrhage which caused admission to hospital

This category included all those in coma or in a semiconscious state with severe neurological signs

Category B—Patients who had completely or partly recovered from the hæmorrhage which caused admission to hospital who were seen within eight weeks of the last bleed, and who were not in danger from the initial hæmorrhage

This category included patients in good general condition, with or without some residual signs of hæmorrhage, but who were still at considerable risk from further hæmorrhage

Finally the patients were subdivided according to the time of inclusion in the trial in relation to the hæmorrhage responsible for their admission to hospital

Table I shows the method of stratification, and the cases in each subgroup There were thus 32 subgroups for each aneurysm The mode of treatment to be adopted was at first determined by a set of previously prepared cards, and later by reference to the relative number in the subgroups treated by each method

Treatment

The patients chosen at random for conservative treatment were transferred, as soon as their clinical state allowed, back to the admitting hospital with a recommendation that they be given a period of six w

TABLE I—METHOD OF STRATIFICATION, AND THE SUBGROUPS

HYPERTENSIVE

Over 50 years								Under 50 years							
Category B				Category A				Category B				Category A			
Interval from hæmorrhage (no of days)								Interval from hæmorrhage (no of days)							
0–3	4–6	7–13	13+	0–3	4–6	7–13	13+	0–3	4–6	7–13	13+	0–3	4–6	7–13	13+
C† O† C† O C O C O C O C O C O C	C† O† C O C O	C† O C O C O O		C†	C† O†	O†		C O† O	C† O	C O O	C† O	O†			

NORMOTENSIVE

Over 50 years								Under 50 years							
Category B				Category A				Category B				Category A			
Interval from hæmorrhage (no of days)								Interval from hæmorrhage (no of days)							
0–3	4–6	7–13	13+	0–3	4–6	7–13	13+	0–3	4–6	7–13	13+	0–3	4–6	7–13	13+
C† O† C† O C O C O C O	C	C† O C O C	C O C O O	O† O†		C† C		C† O C† O C† O C O C O C O C† O C	C† O O	C† O C C	C O	C† C†			

C = conservative treatment O = operative treatment † = death.

complete rest in bed from the date of hæmorrhage We should have preferred to keep these patients under our care, but shortage of beds made this impossible Recurrent hæmorrhage in the cases treated conservatively did not seem to indicate surgery even though it represented a failure of conservative management In 2 cases operation was performed in deference to the strong wishes of the referring physician, but we were advised that for statistical purposes they should be regarded as conservatively treated cases Similarly patients selected for operation who died before surgery could be performed remained in the surgical group

We decided that all surviving patients should be assessed by an independent neurologist after an interval of six months, and that his decision regarding the patients' clinical state should be accepted for purposes of analysis

The ethics of this trial were seriously considered in consultation with senior neurologists and many referring physicians, and it was decided to assess the results at monthly intervals so that the trial could be concluded as soon as a statistically significant difference between the mortalities in any two comparable groups was established Such a difference became apparent in the latter part of 1959, when the trial had been in operation for a little over eighteen months, and as a consequence we immediately altered our policy with regard to aneurysms of the internal carotid artery at or near the point of origin of the posterior communicating artery

The Trial

Patients Included

The cases included in the trial were under our care either at Atkinson Morley's Hospital or the National Hospital, Queen Square, between Jan 1, 1958, and Aug 31, 1959 125 cases of "posterior-communicating" aneurysm were admitted to hospital, of which 31 were excluded from the trial for the reasons given above, and 94 were included in the trial series

The following data, derived from the various subgroups, give a clear picture of the clinical status and comparability of the cases treated surgically and conservatively

Age —Their ages ranged from nineteen to seventy years, but, as previously mentioned, they were divided into those above and below fifty

	Over 50 years	*Under 50 years*
Operation	28	18
Conservative	29	19

Hypertension —As in our previous reports a patient was considered hypertensive if the blood-pressure was 160/90 mm. Hg or above

	Hypertensive	*Non hypertensive*
Operation	21	25
Conservative	21	27

Clinical category —The number of patients in each category was

	Category A	*Category B*
Operation	5	41
Conservative	6	42

Interval before treatment —Finally the interval from the ictus to inclusion in the trial and treatment was

	1–3 days	*4–6 days*	*7–13 days*	*>13 days*
Operation	23	8	10	5
Conservative	25	7	12	4

Results of Treatment

CONSERVATIVE GROUP

To survey the factors influencing mortality in the two treatment groups they must first be viewed separately Table II shows that the expected marked influence of clinical status on mortality, age, and hypertension is of doubtful significance When related to the interval after the ictus the mortality reflects the natural history of the disease, and shows that this can best be assessed from cases admitted within twenty-four hours

TABLE II—PATIENTS TREATED CONSERVATIVELY

Status	Total cases	Deaths
Over 50	29	10
Under 50	19	10
Hypertensive	21	8
Normotensive	27	12
Category A	6	5
Category B	42	15
1–3 days	25	11
4–6 days	7	4
7–13 days	12	4
Over 13 days	4	1

Cause of Death

We found that 2 patients in category A died of the hæmorrhage which caused their admission to hospital In the others death was due to recurrent hæmorrhage This arose in 24 cases—3 in category A, all of whom died and 21 in category B, of whom 15 died The time-intervals of these hæmorrhages were

0–6 days	5 cases	3 deaths
7–10 ,,	7 ,,	6 ,,
10 days or more	12 ,,	9 ,,

When we assessed the influence of rest in bed in relation to recurrent hæmorrhage, we found that the periods of rest for patients without recurrent hæmorrhage were

Rest in bed for 1–2 weeks	3 cases
,, ,, ,, ,, 2–4 ,,	6 ,,
,, ,, ,, ,, 4–6 ,,	21 ,,

In those with fatal recurrent hæmorrhage the duration of rest was, of course, limited, but no case of recurrent hæmorrhage seemed to have resulted from premature mobilisation or discharge, nor was recurrent hæmorrhage apparently related in any way to transferring patients from one hospital to another

Previous Hæmorrhages

To evaluate accurately the number of hæmorrhages before admission to the neurosurgical department we must consider the deaths due to a particular hæmorrhage as opposed to those due to recurrent hæmorrhage Table III shows that two patients admitted after the first hæmorrhage died as a result of it, and that the other deaths in this group were due to subsequent hæmorrhage Similarly 1 patient admitted after the second hæmorrhage died as a result, and the other deaths were due to subsequent hæmorrhage. With these facts in mind we can determine the mortality from each hæmorrhage

TABLE III—OUTCOME IN RELATION TO NUMBER OF HÆMORRHAGES

Hæmorrhage	Total cases	Immediate deaths	Survivors	Recurrent hæmorrhage	Deaths from recurrent hæmorrhage	Total deaths
First	36	2	34	17 (*50%*)	13 (*77%*)	15
Second	8	1	7	6 (*85%*)	3 (*50%*)	4
Third	4	0	4	1 (*25%*)	1 (*100%*)	1
Total	48	3	45	24	17	20

In the group of 36 patients admitted after the first ictus 2 died as a result of the initial hæmorrhage, but this mortality-rate was artificially low because of natural selection and because some gravely ill patients were not transferred by the referring physicians

We should, however, review in more detail the fate of the 34 patients who were admitted after the first hæmorrhage but did not die from it 17 of them had a second hæmorrhage from which 10 died, and thus the mortality-rate was about 60% (10/17) for the second ictus, and 30% (10/34) for all patients at risk Of the 17 patients who had a second hæmorrhage there were 7 survivors 4 of these had a third hæmorrhage, and 3 died, giving a mortality-rate of 75% (3/4) for the third ictus, and 45% (3/7) for all patients at risk The total mortality-rate from recurrent hæmorrhage in this group was therefore 40% (13/34)

Fate of Survivors after Conservative Treatment

Of the 48 patients in the conservatively treated series 28 patients made various degrees of recovery 19 of these were able to return to full work, 6 were partially disabled, and capable of light work only, and 2 were totally disabled The remaining patient is alive but we know no further details about his capacity All these patients were followed up for at least six months, and half of them for a year or longer

SURGICAL GROUP

Table IV shows that clinical status is of major importance, and that age and hypertension are also grave prognostic features The interval between ictus and operation seems to be of little significance until the end of the second week—a fact of no practical importance for by this time over half the fatal recurrent hæmorrhages have occurred

Operative Techniques

The patients selected for surgical treatment fell into two distinct groups

1 Patients who tolerated compression of the appropriate common carotid artery for ten minutes, and who were therefore thought suitable for treatment by ligation of that vessel in the neck

2 Patients who did not withstand compression of the common carotid artery, even after repeated attempts, and who were therefore only suitable for an intracranial operation, such as clipping the neck of the aneurysm and obliterating the sac with clips or by wrapping

For convenience the surgical treatment will be considered in relation to the patient's clinical status

	Total no	*Craniotomy*	*Deaths*	*Carotid ligation*	*Deaths*
Category A	5	5	5 (*100%*)		
Category B	41	4	1 (*25%*)	37	3 (*8%*)

These findings may be compared with the corresponding mortalities in the conservatively treated patients (the conservative cases being grouped according to the operation for which they would have been suitable)

	Total no	*Craniotomy*	*Deaths*	*Carotid ligation*	*Deaths*
Category A					
Operation	5	5	5 (*100%*)		
Conservative	6	6	5 (*83%*)		
Category B					
Operation	41	4	1 (*25%*)	37	3 (*8%*)
Conservative	42	1	0	41	15 (*36%*)

Though the numbers are small, this suggests that the patients in category A did not benefit from surgical treatment

The main question is whether the mortality-rates of 10% (4/41) for surgically treated patients, and 35% (15/42) for conservatively treated cases in category B, differ more than could reasonably be expected by chance. That no such difference exists is called in statistical language the " null hypothesis " For the present data the chance of having 4 deaths or less is 0 0047—i e , less than 1/200 But, in view of the small probability and our conviction that the two groups are not likely to be different except as regards treatment, we must reject the null hypothesis and affirm that operation has reduced mortality and will generally do so in groups subject to the same rules of selection as were the trial group

The effectiveness of carotid ligation can be assessed only by comparison with patients in the conservatively treated control group who were suitable for this operation In fact this leads to rejection of 1 conservatively treated patient and 4 in the surgical group by craniotomy (see figures above) Applying the same reasoning and methods as before, the chance of 3 deaths or less is 0 0027 This small probability shows that in suitable cases carotid ligation reduces the mortality-rate significantly The figures for age and hypertension also show the superiority of surgical treatment in patients under the age of fifty, and in those with normal blood-pressure Patients over fifty and those with hypertension benefited less Gross comparison of the relation between mortality-rate and the

TABLE IV—PATIENTS TREATED SURGICALLY

Status	Total cases	Deaths
Over 50	28	7
Under 50	18	2
Hypertensive	21	7
Normotensive	25	2
Category A	5	5
Category B	41	4
1–3 days	23	5
4–6 days	8	2
7–13 days	10	2
Over 13 days	5	0

interval after the ictus shows no significant difference, and the results of detailed study cannot be assessed statistically (table IV)

Mortality and Morbidity

The deaths in category A suggest that the clinical course of the patients was virtually uninfluenced by surgery, their condition deteriorated steadily until they died

None of the category B patients died of recurrent hæmorrhage All these deaths were attributable to operative interference, the usual cause being insufficient blood-suppy to the hemisphere supplied by the ligated common carotid artery

Complications of Carotid Ligation

Of the 37 patients in category B treated by carotid ligation, 10 had a postoperative hemiplegia or hemiparesis, associated with dysphasia when the dominant hemisphere was affected When the time of operation was related to the incidence of complications no significant reduction in frequency was seen until fourteen days after the hæmorrhage Half the patients were hypertensive while the other half were not, hence hypertension of itself does not predispose to hemiplegia Age, however, seems to be significant, as 8 of the 10 cases which developed hemiplegia were over fifty

Of these 10 patients, 3 died of the complication All 3 were over sixty Of the 7 surviving patients only 3 showed some degree of recovery later

Fate of Survivors

Of 46 patients treated by operation 9 died, giving a total mortality-rate of 20% In category A the surgical mortality-rate was 100%, but in category B only 4 patients (10%) died out of 41 treated Lastly, 3 patients (8%) died out of the 37 treated by carotid ligation The status of the surviving 37 patients is as follows

Craniotomy		*Carotid ligation*	
Full work	2	Full work	27
Partially disabled	1	Partially disabled	5
		Totally disabled	2

When the state of the survivors in this group is compared with that of the patients treated conservatively, we see that the morbidity-rate following operation is somewhat less

	Full work	*Partially disabled*	*Totally disabled*	*Alive—condition unknown*
Operation	29	6	2	
Conservative	19	6	2	1

The proportion of patients who have returned to full work is higher in the surgical group, but it is also true that the 2 totally disabled patients and 4 of those who are partially disabled, became so as a result of common-carotid ligation

Discussion

This carefully designed clinical trial has yielded much information of value, and as, for ethical reasons, it cannot be repeated the results warrant careful study

All the relevant factors show that the cases in the surgically treated and conservatively treated groups are strictly comparable, and that no obvious anomalies arose from the random selection It has been shown that surgical treatment is undoubtedly superior to medical treatment in all patients who are not deeply unconscious, or dying from a compressing intracranial hæmatoma, and carotid ligation can be effectively employed soon after the ictus, giving an excellent measure of protection against recurrent hæmorrhage

As so few patients underwent craniotomy the relative merits of carotid ligation and craniotomy cannot be usefully discussed, but, remembering that complications arose from simple ligation mainly in patients over fifty and that all patients who died were over sixty, we do not think that craniotomy would have yielded better results This does not mean that we have abandoned craniotomy for these lesions, but simply that we must await much more experience before a decision can be made

We are not entirely satisfied with ligation of the common carotid artery, because of its attendant high complication-rate, nor do we know whether there is an optimum time after hæmorrhage when carotid ligation carries the lowest mortality and morbidity rates Though it seems desirable to lengthen this interval the intercurrent deaths from recurrent hæmorrhage may counteract any apparent advantage

Our future efforts, therefore, must be directed towards deciding whether the patient is suitable for a particular type of operation, trying to find the most appropriate time for the procedure, and investigating the factors responsible for postoperative morbidity Only from carefully planned treatment trials will the solutions to these problems be forthcoming Bearing in mind the many unknown factors which operate in the selection of cases for admission to a neurosurgical department, retrospective analysis of patients treated by different surgical methods will probably be of very limited value

Summary

In a series of cases of ruptured aneurysms of the internal carotid artery at or near the point of origin of the posterior communicating artery, the results of surgical and conservative treatment were compared by a carefully controlled trial

Of 94 comparable cases, 48 were treated conservatively and 46 by surgery

The 11 patients in category A (who were likely to die from hæmorrhage) showed no obvious benefit from surgery Of the 83 patients in category B, 42 were treated conservatively and 15 (35%) died Among the other 41 who were treated surgically there were only 4 deaths (10%) Of these 41 patients 37 were treated by common-carotid ligation, with 3 deaths (10%)

The fate of the survivors in both categories indicates a lower morbidity-rate in patients treated surgically

We should like to thank Mr P M Payne, statistician in charge, Royal Marsden Hospital, for his unfailing help in the construction and stratification of this trial, and in compiling the statistical data

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PHOTIC AND SELF-INDUCED EPILEPSY

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THE term "reflex epilepsy" is applied to fits which constantly follow the application of some clearly defined and often stereotyped stimulus It is possible, however, to regard all convulsions as reflex in the sense that the particular pattern of afferent stimuli at a given moment to any epileptogenic area may determine whether it discharges and whether the local discharge is widely propagated The local state of the discharging area will also play an essential part in the provocation of an overt seizure by lowering or otherwise changing the threshold for discharge or its spread A given pattern of afferent stimuli will produce "normal" discharge in normal cortex, while epileptic discharge will occur in the abnormal This view is not novel Indeed such a conception of epilepsy is within limits a logical necessity of viewing the nervous system in terms of reflex activity An essential part of the view is that the *total* afferent situation at the discharging centre has to be considered, and this will determine the timing of a fit

The epileptic fit is a dramatic occurrence both physiologically and behaviourally, and it appears, in isolation at any rate, surprisingly harmless biologically It has therefore come under scrutiny as representing, perhaps in altered form, a biological mechanism with some teleological significance (Chance 1957) If this is so, then it is likely to be invoked compulsively and possibly voluntarily on occasion, and this not uncommonly occurs in light-sensitive epilepsy (Robertson 1954, Van Wulfften Palthe 1959)

One constant characteristic of the seizure, apart from its "paroxysmalness" as Jackson put it, is its interruption of normal behaviour and often of consciousness Consciousness is so important a function that it must be given primary consideration in assessing the biological significance of whatever interferes with it. Where a goal for self-induced epilepsy has been suggested it has been in terms of the possible advantages of reduced or interrupted consciousness (Robertson 1954, Hutchison et al 1958)

In the three cases described here, both these points—epilepsy as a reflex phenomenon and as a goal-seeking process—arise in the analysis of the fits and the setting of their occurrence.

Case-reports

Case 1—A girl, aged 11 years, had had clinical petit-mal attacks for 9 years They consisted of momentary arrest of activity with interruption of consciousness, often brief rolling up of the eyeballs, and occasionally wetting They were first noted only in the summer months when the child was out in bright sunlight and usually just after being exposed to it, when for instance she had been out playing for a few moments Sometimes, however, on suddenly coming into shadow an attack would also occur She was given phenobarbitone and the attacks became fewer During the next few years, however her attacks were noted even when in a room in which sunlight was shining through the window, and they occurred when she was not herself directly exposed to the sunlight A little later she also had one or two attacks on looking directly at an electric light, and a brightly lit television screen even when not particularly flickering was found to induce them She was put on to troxidone and phenytoin sodium and provided with dark glasses, and with these measures her attacks decreased considerably Nevertheless in the following summer they again became more frequent and were particularly bad at school. It was then noticed that when her teacher wore a particularly bright print dress walking in front of the child in a sunny classroom would induce an attack. Her mother also noticed on one occasion that shaking the crumbs from a red-and-white check tablecloth also induced one on a sunny morning Emotional factors probably played some part in the increase, as she was finding her school-work difficult and was worried about examinations Nevertheless, wearing tinted glasses indoors as well as out certainly reduced the attacks and they were always less in dull weather

Full clinical examination, skull X-rays, and lumbar puncture were normal. There was no family history of epilepsy

The resting electroencephalogram (E.E.G) showed occasional bilateral synchronous wave and spike activity at 3 cycles per second. This was increased by overbreathing Photic stimulation was applied at flicker frequencies of 8 to 20 per second At frequencies of 8 to 18 per second, wave-and-spike activity was induced The effect was maximal at 14 per second, and at this frequency a clinical attack was induced.

Comment

Here the initial effective stimulus to attacks was bright sunlight. Then the threshold intensity of the stimulus became less, any bright light being effective Later even brightly coloured objects, if well-lighted, seemed to provoke attacks Possibly other non-photic adjuvant factors in the environment were contributing to the later precipitation, but the clinical effect was of an increase in range of effective stimulus and a reduced threshold for attacks

Case 2.—A girl, aged 18, had for some five years experienced momentary loss of consciousness on exposure to bright sunlight. As the sun first shone into her eyes she would blink once or twice and would then experience a blank for a few seconds for which she had no memory This was not apparent to other people, and she would continue with what she was doing provided it was a well-known activity Thus if eating, conversing, or playing a familiar piece of piano music she would continue to do so Sunlight did not always induce attacks, but they were not infrequent, happening especially in the early mornings She had learnt largely to avoid them by avoiding direct sunlight. Twice in the past two years, these brief attacks had led on to more prolonged loss of consciousness lasting fifteen to twenty minutes, and brief grand-mal attacks had occurred. On both occasions she was being driven along a tree-lined sunlit road at mid-morning On each occasion the sun was on her left and at the same height in the sky On each occasion also she was tired, having been up late the night before, and was emotionally upset. She had travelled this road on many other occasions in bright sunlight and at a similar time of day, but without being tired or upset, and had not had the attacks

The minor attacks were much reduced by phenobarbitone gr I t.d.s , but she was actually taking this when she had her second major attack.

Examination of the central nervous system was negative There was no family history of epilepsy

The E.E.G showed a 10 cycle per second alpha rhythm with interpolated 2, 3 and 4 cycles per second activity Occasional runs of spike-and-slow waves of 3 to 4 cycles per second occurred bilaterally and synchronously and were increased by overbreathing though no clinical attacks were induced. At the patient's request, stroboscopic examination was not attempted.

Comment

In this case interrupted photic stimulation was sufficient of itself to cause minor epilepsy Only, however, when this stimulus was applied in particular conditions of internal and external environment, of which an emotional setting was a part was major epilepsy produced. The total "afferent situation" seemed to be the effective stimulus

Case 3 —A girl, aged $7^1/_2$ years, had for four years had petit-mal attacks associated with interrupted light stimulus The attacks were first noticed to occur when the child ran from shadow into bright sunlight There would be a momentary arrest of movement with staring of the eyes and occasional brief clonic upward movements of the eyeballs Within a year of their onset the child was noticed to be inducing the attacks herself either by deliberately running into bright sunshine or by gazing at the sun and rapidly blinking her eyes Later she would also induce attacks at times by staring at a bright electric light and waving her hand or blinking her eyes Despite adjurations from her parents and teachers the child continued to induce these attacks herself It was noticeable that this behaviour was more frequent at times of emotional stress When she had quarrelled with someone or when things were going badly at school she would tend to indulge in this activity When asked directly, she denied that the attacks were pleasurable, but immediately after an attack she seemed noticeably more relaxed and content On one occasion also during an electroencephalogram session with the stroboscope in which an attack was produced, she expressed a liking for that part of the test

The attacks were reduced but not abolished by troxione and acetazolamide

Examination of the central nervous system, including skull X-rays and lumbar puncture, was entirely negative The mother had had toxæmic fits during pregnancy but otherwise there was no family history of epilepsy

The resting E E G showed spontaneous bursts of bilateral synchronous multiple fast spikes, usually immediately following eye closure, though occasionally with the eyes open Photic stimulation at frequencies between 14 and 20 flashes per second produced after a second or so runs of spikes of much higher voltage On one occasion with the eyes closed, after one second of flashing at 20 per second there was a rapid build-up of spikes and then of bilaterally synchronous 3 per second wave-and-spike activity, which was accompanied by a clinical attack

Comment

The self-induction of these attacks can rightly be described as compulsive at times Despite heated reprimands and threats of punishment the patient would deliberately evade supervision and when she thought herself unobserved induce an attack She gained no apparent advantage from this behaviour, but the outcome appears to have been pleasurable

Discussion

Light-induced epilepsy is of special interest because it provides opportunities for the controlled observation of reflex epilespy in general It is possible to vary the intensity, the flash-frequency, and other measurable qualities of the light source inducing attacks and to establish in certain cases clear parameters for an effective stimulus In other cases, however, such definition does not seem possible, and, in some of them, aspects of the total stimulus situation other than the light itself seem important in provoking an attack Such aspects may include factors in both external and internal environment This problem of the effective stimulus is illustrated in cases 1 and 2

In case 1 the effective external stimulus gradually spread from one in which intense light was essential to one where the photic factor was effective at a much lower threshold and over a wider range of sensory experience Whether this was due to a facilitation or practice effect on the visual pathways which constitute the afferent side of the reflex, or to additional factors such as emotional ones, increasing the sensitivity of the reflex centre is not certain in this case Either mechanism or both could have played a part

Case 2, on the other hand, illustrates the obverse effect Here a light stimulus was effective in provoking petit mal, but only when this stimulus was a part of a particular total stimulus complex, which seemed quite stereotyped for that individual, was it effective in provoking grand mal This case introduces once more the point that the *tout ensemble* of afferent impulses—including exteroceptive and enteroceptive, some of which are the neurological substrate of emotion—arriving at the group of cells initiating epileptic discharge must determine whether firing occurs In this view so-called reflex epilepsy is simply that portion of epilepsy where a readily observed part of the total afferent flow is obtrusive in setting the environment for discharge, and as our methods of investigating afferent impulses improve, so the diagnosis of reflex epilepsy will increase

Case 3 illustrates not only the voluntary induction of epilepsy, but also the compulsive nature that such behaviour may assume Why such activity should become compulsive is a matter of some interest Possibly the reduction or abolition of cortical activity may at times be pleasurable, and it is noteworthy that the majority of the drugs of addiction are in fact selective cerebral depressants Normal cortical activity is certainly reduced during a petit mal seizure Others have remarked on the general similarity of this pattern of behaviour to that of compulsive masturbation in children (Hutchison et al 1958), and it would be of value to know whether the E E G during the orgasm also showed any evidence of specific change of cortical activity

Loss of consciousness may be viewed as at times a biological protection for the organism when intensely unpleasant stimuli occur in a setting where other and more usual avoiding reactions are not possible It may also have a more personal value in certain neurotic responses, and some cases of self-induced epilepsy may be interpreted in this light Epilepsies, including grand mal, may also be considered as parts of a more primitive behaviour mechanism, which in animals is of biological value in relation to avoidance of trauma and escape from danger (Chance 1957, 1959) The functional linking of the motor components of such behaviour, achieved by natural selection, will mean that in organisms at a higher level of the evolutionary scale a stimulus evoking one component appropriately may also evoke others inappropriately The original biological significance of the response may then be hard to recognise In animals the setting and content of such " epileptic " behaviour seem to relate it to hypothalamic activation In man there is growing evidence of the subcortical origin of many epileptic discharges, even of some in which cortical abnormality can also be found though direct manifestations of hypothalamic activity are seen more in epileptic variants such as narcolepsy, the akinetic attack, and the visceral and vasomotor elements of petit mal or temporal lobe epilepsies Even if we discount any direct homology between animal and human epilepsy, it is worth considering the latter not only as a clinical abnormality, but as containing elements of some biologically purposive reaction On such a view the total situation which provokes a fit may shed new light on both causation and prevention

My thanks are due to Dr R G Willison for helpful criticism of this paper

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THE HYPOTENSIVE ACTION OF DIURETIC AGENTS

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THE synthesis of chlorothiazide (6-chloro-7-sulphamyl-1,2,4,-benzothiadiazine-1,1-dioxide) provided clinicians with a powerful oral diuretic agent (Novello and Sprague 1957). Its main action appears to be interference with tubular reabsorption of sodium and chloride (Beyer et al. 1957), together with mild inhibition of carbonic anhydrase. This results in a marked increase in the urinary excretion of sodium and chloride, and a decrease in the excretion of potassium and bicarbonate.

The diuretic potency of chlorothiazide was demonstrated clinically (Ford et al. 1957) and later found to compare favourably with the activity of the parenteral organic mercurial diuretics (Ford et al. 1958, Bayliss et al. 1958).

Almost simultaneous investigations (Hollander and Wilkins 1957, Freis and Wilson 1957, Tapia et al. 1957) revealed that chlorothiazide was a valuable hypotensive agent, both alone and in combination with other hypotensive drugs. This has been confirmed on a number of occasions (Heider et al. 1958, Barnett and Marshall 1958, Wilkins 1958, Hall and Owen 1959). Evidence as to the mode of action of chlorothiazide in hypertension is conflicting. In nonœdematous hypertensive patients lowering of the blood-pressure has been associated with a reduction in the amount of extracellular water and sodium (Wilson and Freis 1958), but this was not confirmed by Winer (1958), and other investigators think that the drug may have an additional specific effect (Wilkins 1957, Hollander et al. 1959). A reduction in plasma-volume has also been shown to accompany enhancement of the activity of ganglion-blocking drugs (Dustan et al. 1959, Dollery et al. 1959).

A more recent analogue—hydrochlorothiazide—has been found to be between ten and twenty times as potent a diuretic agent as chlorothiazide (Richterich 1958, Ford 1959, Fleming et al. 1959, Moyer 1959). This dosage ratio appears to be applicable also to their hypotensive actions (Vertes and Sopher 1959, Smirk et al. 1959).

The present study was designed to illustrate the relation between the diuretic and the hypotensive effects of chlorothiazide and hydrochlorothiazide in nonœdematous hypertensive patients. The effects of the two drugs were compared with those of the mercurial diuretic, mersalyl. More detailed observations including plasma-volume and thiocyanate-" space " estimations, were made in a smaller group of patients receiving hydrochlorothiazide.

Methods

The subjects were hypertensive patients without evidence of heart-failure. Most were outpatients and all were on a free diet with an uncontrolled sodium and fluid intake. Before admission to the trial, each patient was familiarised with the staff and procedures, including multiple blood-pressure recordings, employed at the clinic.

Five recordings of the blood-pressure were made in the sitting and standing postures between 9 A.M. and 12 noon. The mean pressure was obtained by summing the systolic and diastolic readings and dividing the total by 10. The alterations in blood-pressure are actual changes and not percentages of the initial level. The patient had been receiving placebo tablets, and when the blood-pressure appeared stable three twenty-four-hour urine samples were collected and the initial mean blood-pressure recorded. The diuretic was then given for three days during which further twenty-four hour urine samples were collected. Mean blood-pressures were recorded on days 1 and 3.

The dosage schedules were: chlorothiazide 0·5 g. twice daily, hydrochlorothiazide 50 mg. twice daily, mersalyl 2 ml. daily.

In 11 patients the plasma-volume, thiocyanate space, packed-cell volume, serum sodium and potassium, and weight, were measured before, and seven days after, the addition of hydrochlorothiazide.

In a further group of 19 patients comparison was made between hydrochlorothiazide and mersalyl.

The plasma-volume, and extracellular-fluid estimations were carried out in the fasting patient at 8.30 A.M. Estimations of plasma-volume were performed using azovan blue *B.P.* (Evans blue *U.S.P.*) according to the method described by Steinbeck (1950), collecting serial blood samples over a period of sixty minutes and calculating zero time by a mathematical extrapolation.

Thiocyanate space was estimated on samples withdrawn 120, 125, and 130 minutes after administration of approximately 20 ml. of a 5% solution of sodium thiocyanate.

Syringes were weighed before and after injection of both azovan blue and thiocyanate.

The creatinine clearance determinations were performed in duplicate, using Owen's (1954) method of estimating the true plasma-creatinine level.

The initial heights and weights were recorded and the surface area calculated from the nomogram of Dubois and Dubois. The creatinine clearance, together with alteration in urinary volume and electrolyte excretion, in plasma-volume, and extracellular-fluid space, have all been expressed in units per sq. m. surface area.

The basal blood-pressure was recorded during sedation with pentobarbitone as recommended by Smirk (1957). The supplemental blood-pressure was derived from the difference between the basal pressure and that observed in the clinic.

Results

Observations were made on the hypotensive and diuretic activity of chlorothiazide in 16 patients, hydrochlorothiazide in 30, and mersalyl in 16. After treatment with any of these drugs for three days, there is a reduction in blood-pressure (shown in table I together with the average increase in renal elimination of water, sodium, and potassium during three days' treatment). The blood-pressure changes after one day's treatment were similar but smaller.

There was no significant difference between the blood-pressure fall produced by chlorothiazide or hydrochlorothiazide and that produced by mersalyl. Nor was there a

TABLE I—EFFECT OF THREE DAYS' TREATMENT WITH CHLOROTHIAZIDE, HYDROCHLOROTHIAZIDE, AND MERSALYL ON BLOOD-PRESSURE AND AVERAGE INCREASE IN EXCRETION WATER, SODIUM, AND POTASSIUM

Drug and no. of patients	Initial B.P. (mm. Hg)	B.P. drop (mm. Hg)	Increased renal excretion per sq. m. surface area		
			Water (ml.)	Sodium (mEq.)	Potassium (mEq.)
Chlorothiazide *(16)*	151 ± 15·6	14 ± 10·1	235 ± 22·1	43 ± 13·4	12 ± 7·7
Hydrochlorothiazide *(30)*	152 ± 19·2	18 ± 9·4	272 ± 17·4	41 ± 18·8	11 ± 7·6
Mersalyl *(16)*	152 ± 19·6	18 ± 9·5	293 ± 16·6	31 ± 20·6	5* ± 8·5

* The figure for the potassium excretion is relatively high because of one patient in whom mersalyl induced an average increase in excretion of 28 mEq. per day.

significant difference between the increase in water and sodium excretion produced by any of these agents

Mersalyl, as would be expected, had a much smaller effect on potassium excretion than either chlorothiazide or hydrochlorothiazide With the latter two drugs no difference in potassium loss could be detected

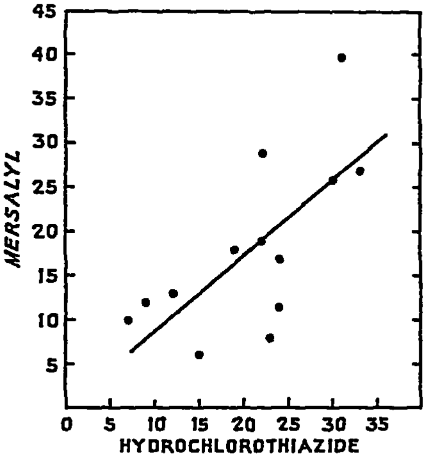

Fig 1—Comparison of falls in blood-pressure after 3 days' treatment with mersalyl (2 ml intramuscularly daily) and with hydrochlorothiazide (100 mg daily) r=0 69

Although a fall in blood-pressure was evident with each diuretic agent, analysis of regression did not demonstrate a significant relation between this fall and the increase in fluid, sodium, or potassium excretion, or between blood-pressure fall and initial blood-pressure

In 13 patients comparison of the effects of hydrochlorothiazide and mersalyl at the same blood-pressure level was possible, 7 receiving hydrochlorothiazide first and 6 mersalyl first (6 other patients had to be excluded because the blood-pressure did not return to its original levels within a practicable time The effects of a three-day course may be apparent for as long as three weeks) The effects of the two chemically dissimilar diuretic agents on the fall in blood-pressure and the increase in water and sodium excretion are compared in figs 1–3 With both drugs a high degree of correlation between these two effects is seen in every case It seems that, for the individual patient, a characteristic diuretic response is accompanied by a characteristic blood-pressure response

The relation of the blood-pressure response to alterations in plasma-volume and extracellular fluid (measured by the thiocyanate space) was studied in a further 11 patients before and after a week's treatment with hydrochlorothiazide (One thiocyanate reading was discarded for technical reasons) Except for 1 patient in whom the plasma-volume increased slightly, all showed a reduction in plasma-volume However, the fall in blood-pressure did not correlate significantly with the plasma-volume contraction

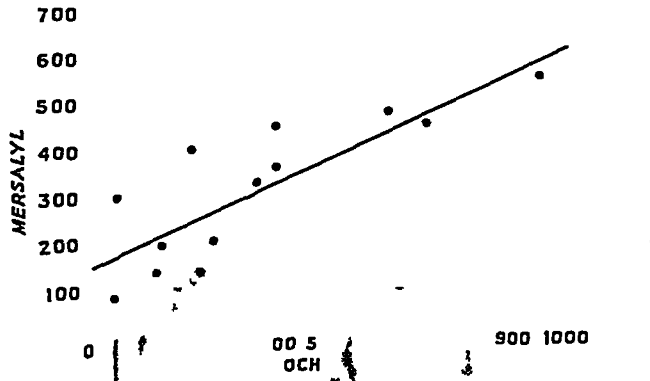

Fig 2—Co surface daily) an era ml per sq m ersalyl (2 ml y) r=0 80

All patients showed a reduction in thiocyanate space. When the fall in blood-pressure was plotted against this decrease (fig 4), a probably significant relationship was apparent The individual values for initial blood-pressure and blood-pressure fall, reduction of plasma-volume and of thiocyanate space, fall in body-weight and reduction of surface area, are shown in table II The correlations between (*a*) the reduction in plasma-volume and thiocyanate space (r=0 72, P=0 02) and (*b*) the reduction in thiocyanate space and body-weight (r=0 84, 0 01>P>0 001) seem to confirm the validity of the methods employed

The serum-sodium level, although varying in some cases, did not show the overall reduction seen with the serum-potassium Some hæmoconcentration can be inferred from the increase in packed-cell volume (table III)

Fig 5 shows the alteration in the blood-pressure in 5 patients following infusion of 6% salt-free dextran in a quantity the same as the estimated reduction in plasma-volume Immediately after this infusion, the blood-pressure returned to approximately its pretreatment value

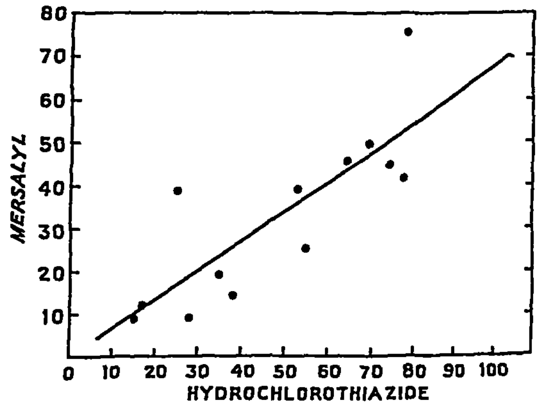

Fig 3—Comparison of the average daily increase in sodium excretion (mEq per sq m surface area) following 3 days' treatment with mersalyl (2 ml daily) and with hydrochlorothiazide (100 mg daily) r=0 81

As the three diuretic agents in the dosage given appeared to have comparable hypotensive activity, the whole group was considered together, and the relation of blood-pressure fall to various other factors was examined

There was no correlation between blood-pressure fall and either initial blood-pressure, or basal blood-pressure However, there was a quite significant (0 05>P>0 02) correlation between the fall and the "supplemental" blood-pressure Blood-pressure fall was not significantly related to age or weight

There was no correlation between the blood-pressure fall and the creatinine clearance But, somewhat surprisingly, there was a highly significant *negative* correlation between the creatinine clearance and the increase in fluid excretion (P<0 001) This was contributed to mainly by the mersalyl group (P<0 001), the hydrochlorothiazide and chlorothiazide groups having non-significant negative regression coefficients

The urine pH rose both with chlorothiazide and with hydrochlorothiazide—more with the former—but did not alter significantly with mersalyl As there is no concise method of grouping these results, the values have not been included

Discussion

Chlorothiazide has established itself as a potent oral diuretic agent of very low toxicity When used for

TABLE II—RELATION BETWEEN BLOOD-PRESSURE DROP FOLLOWING ONE WEEK'S TREATMENT WITH HYDROCHLOROTHIAZIDE (50 MG TWICE DAILY) AND DIMINUTION IN PLASMA-VOLUME, EXTRACELLULAR-FLUID VOLUME, AND BODY-WEIGHT

Patient no	Sex	Initial B.P	B.P drop (7 days)	Plasma-volume			Thiocyanate space			Initial weight (kg)	Weight drop (kg)	Surface area (sq m.)
				Before	After	Difference (ml per sq m.)	Before	After	Difference (litres per sq m.)			
1	M	159	14	3211	2847	193	19,650	17,720	1·02	75·3	2·3	1·89
2	M	177	−2	2948	3076	−75	18,641	17,950	0·40	60·7	0·4	1·71
3	M	144	23	3544	3386	80	19,971	18,074	0·96	82·5	2·0	1·98
4	M	144	19	3606	3329	142	19,441	16,830	1·34	89·0	2·0	1·95
5	F	141	14	3690	3372	166	19,212	17,229	1·04	83·2	2·1	1·91
6	F	122	13	3210	2992	123	18,400	17,090	0·74	72·3	1·2	1·77
7	M	148	20	3368	3150	138	16,320	15,172	0·73	55·0	1·5	1·58
8	M	144	24	3845	3207	319	21,473	18,312	1·58	87·5	5·4	2·00
9	M	139	5	3717	3344	230	16,550	14,731	1·12	59·0	1·0	1·63
10	F	120	8	2546	2344	149	13,614	13,131	0·36	43·1	0·0	1·36
11	F	154	18	2212	2110	63				63·5	1·5	1·61

removing œdema fluid from patients with hypertensive heart-failure, it was found also to lower the blood-pressure. Considerable hypotensive activity was then demonstrated in nonœdematous hypertensive patients, and chlorothiazide, together with its recently synthesised and more powerful analogue hydrochlorothiazide, has since proved very useful in the management of high blood-pressure (Smirk et al. 1959).

TABLE III—EFFECT OF ONE WEEK'S TREATMENT WITH HYDROCHLOROTHIAZIDE (100 MG DAILY) ON THE SERUM SODIUM AND POTASSIUM AND THE PACKED-CELL VOLUME (11 PATIENTS)

—	Before	After	Alteration
Serum Na (mEq.)	142·2±6·0	142·1±9·8	Not significant
Serum K (mEq.)	4·9±0·11	4·1±0·13	0·02>P>0·05
P.C.V.	43·5±5·1	45·5±5·5	P=0·001

The relation between the diuretic and hypotensive effects of these drugs has a possible bearing on the pathogenesis of hypertension. The present study shows that their reduction of blood-pressure is not significantly related to the increase in excretion of water, of sodium, or of potassium. This might suggest that they have a specific hypotensive action in addition to their diuretic action. However, the organic mercurial mersalyl can be seen to have an entirely comparable effect. When the hypotensive responses of the individual patient to hydrochlorothiazide and to mersalyl were compared, they resembled each other closely and were associated with very similar increases in excretion of water and sodium. Though different people seem to differ widely in their response to diuretic agents, the same person responds in much the same way to different agents.

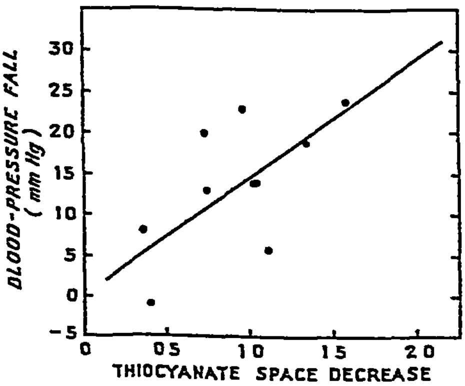

Fig. 4—Correlation between blood-pressure fall (mm Hg) and decrease in the extracellular fluid (thiocyanate space litres per sq m.) following 7 days treatment with hydrochlorothiazide (100 mg daily). r=0·72.

Wilkins et al. (1958) demonstrated the hypotensive action of intravenous mercaptomerin, and the same group have published (Hollander et al. 1959) data which agree with our own observations—namely, that in hypotensive patients whose blood-pressure fell with mercurial diuretics it also fell with chlorothiazide.

A sharp diminution of plasma-volume (Dustan et al. 1959, Dollery et al. 1959) and of plasma-volume and extracellular-fluid volume (Wilson and Freis 1958) has been recorded after administration of chlorothiazide. But a return to pretreatment values was noted after long-continued therapy (Wilson and Freis 1958); indeed after six to eight weeks Winer (1958) could find no significant changes either in the plasma and extracellular-fluid volumes, or in the total exchangeable sodium and total body-water. Similarly Murphy (1950) found no relation between the fall in blood-pressure and the reduction in plasma-volume caused by a low-salt diet.

After seven days' treatment with hydrochlorothiazide we found a reduction in plasma-volume in 10 out of 11 hypertensive patients. However the regression of blood-pressure fall on decrease in plasma-volume was not statistically significant.

On the other hand relating blood-pressure fall to reduction in thiocyanate space (10 cases) gave a regression coefficient (r=0·63—8 d.f.—0·1>P>0·05) indicating a probably significant relationship. The modification of such additional factors as tissue turgidity might perhaps account for this result.

In 4 patients restoration of pretreatment blood-volume by infusion of dextran also restored the blood-pressure to near pretreatment levels.

It seems likely, then, that in an individual hypertensive patient reduction in plasma-volume may produce a

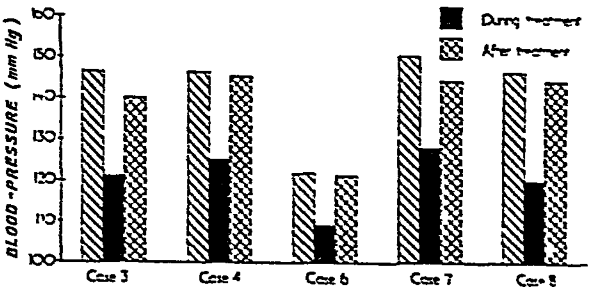

Fig. 5—Fall in blood-pressure in five patients after 7 days treatment with hydrochlorothiazide (100 mg daily) and response to infusion of salt-free dextran to replace the measured reduction in plasma-volume.

characteristic fall in blood-pressure, but that when a group of patients are examined the reduction in plasma-volume is not strictly related to the hypotensive response

That restoration of blood-volume with dextran infusions can abolish the sensitising effect of chlorothiazide on ganglion-blocking agents has been shown in both hypertensive (Dollery et al 1959) and normotensive subjects (Wanko and Freis 1958)

The validity of the plasma-volume and thiocyanate-space estimations was attested by the significant relations between the reduction of each and between fall in total body-weight and the reduction in thiocyanate space

Taking all three diuretic groups together, no significant correlation was observed between the hypotensive responses and the severity of the hypertension as suggested by the basal blood-pressure or the height of the initial pressures There did appear, however, to be a correlation between the hypotensive response and the "supplemental" blood-pressures—i e, the difference between the "casual" (in this case the initial) and the "basal" blood-pressures This suggests that the fraction of the blood-pressure affected by diuretic agents is that superadded by the patients' reaction to the environment at the time the pressure is measured (Smirk 1957) rather than the fundamental or basal hypertensive state There was no correlation with the patients' age or weight

To sum up, it seems likely that chlorothiazide and hydrochlorothiazide reduce the blood-pressure in hypertensive patients by their diuretic action, and that the reduction of blood-pressure is a characteristic response of the individual to diuresis rather than to a particular drug The fall in blood-pressure induced by diuresis is brought about, at least in part, by reduction in plasma-volume, supplemented perhaps by concomitant diminution in tissue fluids

Additional evidence against a specific hypotensive effect of chlorothiazide is provided by animal experiments (E G M., unpublished) which did not show any vasodepressor effect in perfused rat hindquarter or isolated arterial strip preparations

Much interest is being taken in the comparative potency of chlorothiazide and hydrochlorothiazide Our results suggest that with the dosage used (chlorothiazide 1 0 g per day, hydrochlorothiazide 0 1 g per day) there is no practical difference in their efficacy either in reducing the blood-pressure or in increasing the renal excretion of water, sodium, or potassium in the nonœdematous hypertensive patient Other investigators have pointed out that hydrochlorothiazide has less effect on pH and bicarbonate excretion The action of mersalyl (2 ml daily) is similar except that it has little effect on potassium excretion However the considerable loss of potassium in one patient confirms the observations of Cort and Matthews (1954) that serious depletion may occasionally be induced by the organic mercurial diuretics After three days' treatment with any of three powerful diuretic agents the blood-pressure may take one to three weeks to return to pre-treatment levels

It is of interest that, within the considerable range of renal function in our patients, the hypotensive responses were not related to the creatinine clearance. Even more surprising, perhaps, was the significant inverse relation of creatinine clearance to fluid excretion, seen particularly in the mersalyl group No similar relation was evident between creatinine clearance and sodium excretion

Summary

Chlorothiazide, hydrochlorothiazide, and mersalyl were found to produce equivalent hypotensive responses in a group of nonœdematous patients

In the group as a whole there was no significant relation between the fall in blood-pressure and the increase in the renal excretion of water, sodium, and potassium In the individual patient, however, the fall in pressure corresponded to the increase in the renal excretion of water and sodium, whether this was produced by mersalyl or hydrochlorothiazide

There appeared to be a significant relation between the fall in blood-pressure and the reduction in the extracellular-fluid volume

Lowering of blood-pressure was also associated with a reduction in plasma-volume, and in individual patients restoration of plasma-volume with salt-free dextran restored the blood-pressure approximately to the pre-treatment levels for that patient

In doses of 1 g and 100 mg per day respectively, chlorothiazide and hydrochlorothiazide had closely equivalent effects on electrolyte excretion

We wish to acknowledge the encouragement and advice of Sir Horace Smirk. One of us (R B I M) receives a grant from the Medical Research Council, New Zealand

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"It is not for disease or diseases in the abstract that provision has to be made, but for persons liable to or suffering from disease The first essential for the proper and efficient treatment of individual persons is, therefore, not institutional but personal service, such as can be rendered to the people in their own homes only by a family doctor who has the continuous care of their health, to whom they will naturally turn for advice and help in all matters pertaining thereto, who will afford them such professional services as he can render personally, and who will make it his duty to see that they obtain full advantage of all the further auxiliary services that may be otherwise provided."—*Report to Scottish Board of Health from its Consultative Council on Medical and Allied Services* 1920

ABNORMALITIES INVOLVING THE X CHROMOSOME IN WOMEN

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Jacobs and her colleagues (1959a) have published evidence for the existence of a human "super-female" with a sex-chromosome complement of XXX, the patient presenting as a case of secondary amenorrhœa Ford et al (1959a) have shown that chromatin-negative patients with Turner's syndrome have an XO sex-chromosome complement. We report here two new abnormalities which involve the X chromosome in women with amenorrhœa, and record data on a second "super-female"

The case-records are given in detail as the study of these patients raises important considerations, particularly in the clinical investigation of patients with persistent amenorrhœa. Each patient was identified as possibly having a sex-chromosome abnormality from a study of the sex chromatin in buccal mucosal cells

Case-reports

FIRST CASE

Clinical Data

The patient, a phenotypic female, was first seen by one of us (J G) because of anginal pain. It was found from her history that she had never menstruated, and one of us (H G C.) noted that some of the buccal mucosal cells contained two sex-chromatin bodies The patient was born in 1908, her father being 30 and her mother 32 years old at her conception. She is the fifth child in a sibship of six, her three elder brothers and her younger brother being married with families Her sister, who died at the age of 24, had been married for fifteen months but had had no children.

The appearance of the patient is shown in fig 1, and is noteworthy for the absence of breast development, the length of the arms, and the masculine character of the upper trunk and shoulder-girdle Her height is 5 ft 1 in and her arm span 5 ft. 7 in. Her crown-to-pubis and pubis-to-sole measurements are 2 ft. 6 in and 2 ft. 7 in. respectively X-ray examination reveals that not only are the dimensions of the bones of her shoulder-girdle those of a male, but her pelvis is android in shape, with its size and bone texture of male rather than female appearance.

The patient, whose aptitudes are feminine, is of low normal intelligence Her head hair line is masculine, her pubic hair is of the normal female type, but her axillary hair is very scanty The external genitalia are under-developed with the exception of the clitoris, the labia majora being small and the labia minora vestigial. She has several deeply pigmented nævi on her face and neck, but no other stigmata of Turner's syndrome. The vagina is absent and no uterus is palpable.

TABLE I—CASE 1 CHROMOSOME COUNTS

Tissue	Total no of cells	Chromosome number					
		<44	44	45	46	47	>47
Sternal marrow	69	2		67			
Blood	100	3	9	71	5	11	1
Skin lt shoulder	48			18	2	28	
Skin rt leg	36		1	15		20	
Totals	253	5	10	171	7	59	1

Blood-group studies have been made by Dr Sylvia Lawler, of the Galton Laboratory, University College of London, and the findings are as follows

$A_1(\beta)$ MN Ss R_1R_1.P– Le(a– B–) K–
Lu(a–) Fy(a– b–) Jk(a– b–) Non-secretor ABH

Colour-vision and hormone-excretion studies together with palm-print analysis are being made and will be reported later

Nuclear Sex

Examination of smears from the buccal mucosa showed the proportion of cells with sex chromatin to be unusually large. 52% of cells contained a single body and 37% two bodies In our hands in normal women the mean percentage of cells with a single body is 41 (S.D 3 4), and cells with two chromatin bodies have never been seen. In contrast the neutrophil polymorphs were of the male type and no "drumsticks" were seen in 1500 neutrophils (Davidson and Robertson Smith 1954)

Chromosome Analysis

Several different tissues were examined. Chromosome preparations were obtained from the sternal marrow by the method of Ford, Jacobs, and Lajtha (1958), from the peripheral blood by an adaptation of the method of Hungerford et al. (1959), and from two skin samples, one from the left shoulder and one from the right leg, by the method of Harnden (1960) The chromosome counts are shown in table I

Analysis of cells with 47 chromosomes from all cultures revealed a constant abnormality due to the addition of a chromosome in the medium-size range where the X chromosome is found. Analysis of cells with 45 chromosomes con-

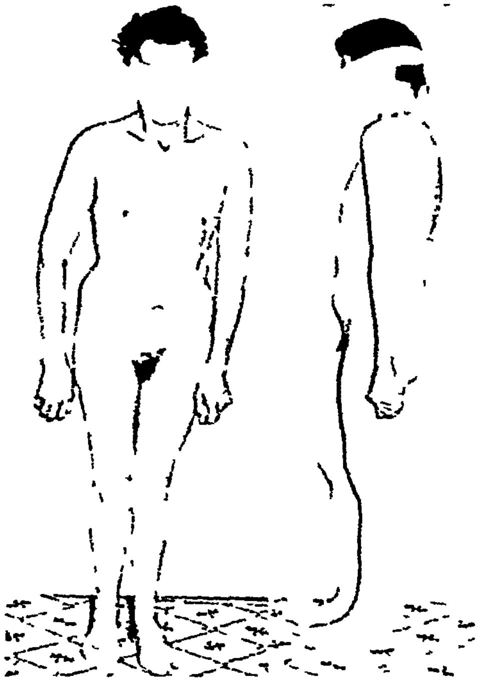

Fig 1—Case 1 present appearance of patient.

sistently showed a chromosome in the same range to be absent In view of the finding of double chromatin bodies in the buccal mucosal cells and the absence of "drumsticks" on the polymorphs, the cells with 47 chromosomes are considered to have an XXX sex-chromosome complement and those with 45 an XO complement In contrast analysis of the seven cells with 46 chromosomes failed to show a consistent pattern, and these are therefore presumed either to be cells with 47 chromosomes from which 1 has been lost during preparation, or cells with 45 chromosomes which have acquired an additional chromosome from a neighbouring broken cell Similarly no consistent pattern was found in cells with counts of less than 45

In both skin samples the majority of cells had 47 chromosomes The high proportion of cells from the buccal mucosa with double chromatin bodies suggests that the cells in this site are mostly of the XXX type

The leucocytes from the peripheral blood also show an admixture of two cell types, the majority containing 45 chromosomes with an XO complement In contrast the bone-marrow appears to contain only cells with 45 chromosomes The discrepancy between the blood and bone-marrow may be explained in at least three ways Firstly the marrow may consist only of cells with 45 chromosomes, but the lymph-nodes and other sites in the reticuloendothelial system may contain cells of the other type Secondly the marrow sample may not have been representative of the marrow as a whole, which in other areas may contain cells of the alternative stem-line Finally, it is possible that only the marrow cells with 45 chromosomes proliferated in culture The first explanation seems to us the most likely as it is a reasonable supposition that some of the dividing cells found in blood-cultures are derived from the lymph-nodes and other sites in the reticuloendothelial system

Comment

Ford et al (1959b) have described a presumptive XX/XXY mosaic in a phenotypic male with Klinefelter's syndrome, and Ford (1959) has reported several phenotypic females with Turner's syndrome whom he considers to be XO/XX mosaics

The evidence now presented suggests that our patient is a mosaic whose body is composed of cells some with 47 and some with 45 chromosomes, and with sex-chromosome complements respectively of XXX and XO Although we have no evidence for the presence of cells with 46 chromosomes and a sex-chromosome complement of XX, and while their existence seems unlikely, such cells may be present in tissues not examined

Assuming that our patient is a 45/47 mosaic, the most likely explanation for this is that non-disjunction of the X chromosomes occurred during the first-cleavage division in a normally constituted zygote Thus instead of producing two daughter cells each with 44 autosomes and two X chromosomes, cell division resulted in two unlike daughter cells, one with 44 autosomes and three X chromosomes and one with 44 autosomes and a single X chromosome

It is theoretically possible for mosaicism to arise at any stage of development, but had this error occurred at a later stage than the first-cleavage division it would have given origin to a triple stem-line mosaic composed of cells with 45/46/47 chromosomes and with sex-chromosome complements XO/XX/XXX Probably not only will the composition of the mosaic be affected by the stage at which the divisional error occurs, but this may have important repercussions on the ultimate form of development of the individual

SECOND CASE

Clinical Data

This patient was first seen by one of us (T M) in 1947 with primary amenorrhœa She was born in 1923, her father being 27 and her mother 22 years old at her conception The patient is the eldest in a sibship of four, her brother is married with one child, and both sisters menstruate regularly Her height is 5 ft 1 in and her arm span 5 ft $3^1/_2$ in Both her crown-to-pubis and pubis-to-sole measurements are 2 ft 7 in She weighed 8 st 1 lb in 1947 but since marriage in 1949 her weight has increased to 14 st 4 lb

The patient, whose aptitudes are feminine, is of low normal intelligence When first seen she had scanty pubic and axillary hair, no breast development, and infantile external genitalia, no other external abnormalities were present. Œstrogen therapy produced some vaginal bleeding, along with breast development and increased growth of pubic and axillary hair

At laparotomy the uterus was found to be under-developed and the gonads to be "streaks" of rudimentary tissue, ovaries were not seen in the normal sites nor were testes found. Histologically one gonad was composed of ovarian tissue in which only a few primitive follicles were found, but the tissue of the other was not recognisably ovarian

Colour-vision and hormone-excretion studies together with palm-print analysis are being made and will be reported later

Nuclear Sex

Examination of buccal smears on three occasions showed sex chromatin in only 7% of the cells Altogether 500 cells were studied, and in only 36 was a chromatin body found Not only was the proportion of chromatin-positive cells very low, but before the patient's chromosome constitution was known the chromatin bodies were noted by one of us (N M) as being

TABLE II—CASE 2 CHROMOSOME COUNTS

Tissue	Total no of cells	Chromosome number					
		<44	44	45	46	47	>47
Sternal marrow	25	2	1	1	21		
Blood	103	3	2	7	87	4	
Skin lt thigh	24		2	4	18		
Skin rt thigh	34		4	2	26	2	
Left gonad	15		2	2	11		
Right gonad	13			2	11		
Totals	214	5	11	18	174	6	

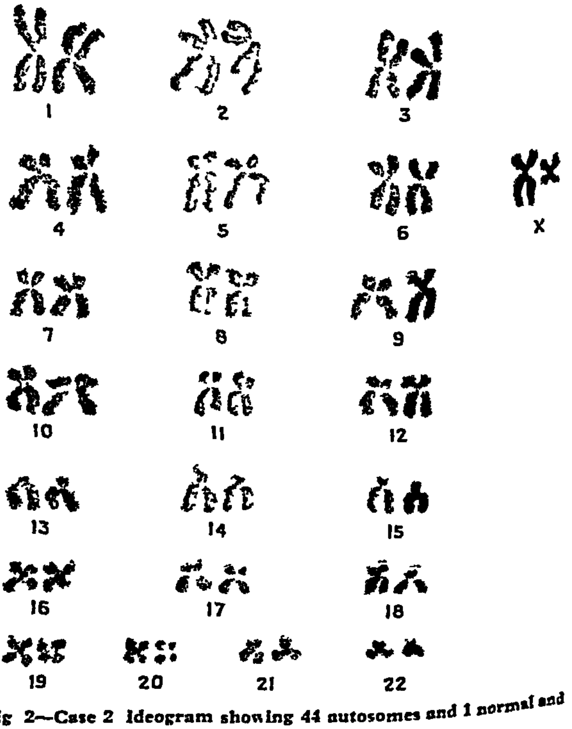

Fig 2—Case 2 Ideogram showing 44 autosomes and 1 normal and 1 abnormal X chromosome

smaller than usual. In blood films no "drumsticks" were found on 1000 polymorphs. These findings were regarded as equivocal.

Chromosome Analysis

Sternal marrow, the leucocyte component of peripheral blood, two skin samples—one from the left and one from the right thigh—and material from both gonads were cultured. The chromosome counts are shown in table II.

In all tissues the modal number was 46, and counts differing from this are considered mainly to be artefacts arising during the preparation of the cells (Court Brown, Jacobs, and Doll 1960). Thirty-four of the cells with 46 chromosomes, representing all of the tissues cultured, were analysed and all showed a constant morphological abnormality (fig. 2). There was an additional small submetacentric chromosome similar to autosome 16 of the normal complement, and 1 chromosome was absent from the range in which the X chromosome is found. These findings together with those of the nuclear sex as seen in the buccal smears, which was consistent neither with an XX constitution nor with an XO constitution, are interpreted as being due to an abnormality of one of the X chromosomes. We have found the length of the X chromosome in normal individuals to vary from 4·78% to 5·67% of the total haploid autosome length with a mean value of 5·34%. In this patient the apparently normal X chromosome, measured in four cells, varied from 4·82 to 5·66% (mean 5·35%) and the abnormal X only from 2·83 to 3·42% (mean 3·22%) of the total haploid autosome length. Measurement of the autosomes showed them to be within the normal range for length and arm ratio. The most reasonable explanation for the significant reduction in the length of the abnormal X chromosome is that part of it has been deleted.

Two other explanations, however, require consideration. First, the patient might have an XO sex-chromosome constitution together with an additional small submetacentric autosome or part of an autosome. We feel, however, that this explanation can be dismissed for four reasons. Firstly, apart from deficient breast development, infantile genitalia, and the primitive appearance of the gonads, no other stigmata of Turner's syndrome were found; secondly, if she had an XO constitution the buccal smear should be chromatin-negative; thirdly, in the other two conditions known to be associated with an extra autosome multiple-system abnormalities are present (Lejeune et al. 1959, Jacobs et al. 1959b, Edwards et al. 1960); and fourthly this consideration requires two non-disjunctional errors to have occurred at the same time. The second possibility is that the small submetacentric chromosome is a Y chromosome with part of an X chromosome attached. This situation could arise if a segmental interchange occurred during spermatogenesis between the X and Y chromosomes. There are three reasons for dismissing this explanation. Firstly it would seem most unlikely that a tiny fragment of the X chromosome would nullify the masculinising effects of the Y, particularly as patients with an XXY constitution are phenotypic males. Secondly, those phenotypic females who are sex-reversed males with an XY constitution have been shown so far to be cases either of testicular feminisation or of pure gonadal dysgenesis (Jacobs et al. 1959c, Harnden and Stewart 1959) and the features of this case conform with neither of these conditions. Thirdly, some of the gonadal tissue was histologically recognisable as ovarian, but none as testicular tissue.

Comment

We presume that this patient is uniformly composed of cells containing one normal and one abnormal X chromosome, and that the latter is abnormal because a segment has been deleted; in consequence it is most likely that the causative error occurred during gametogenesis in one or other parent. It is reasonable to postulate the existence of a range of variation, depending on the size of the deletion, from the normal woman with two X chromosomes to the phenotypic female with an XO constitution. Consideration of the clinical and cytological findings in this patient suggest that she occupies an intermediate position in the range. Finally we must not overlook the possibility that a male may also carry a partially deleted X chromosome.

TABLE III—CASE 3 CHROMOSOME COUNTS

Tissue	Total no. of cells	Chromosome number					
		<44	44	45	46	47	>47
Blood	32			1	2	29	
Skin	29			2	2	25	
Totals	61			3	4	54	

THIRD CASE

Clinical Data

During a routine survey of the nuclear sex of the inmates of an institution for mental defectives, a phenotypic female was found to have double chromatin bodies in her buccal mucosal cells. This woman was born in 1939, but no details are known of her family history.

The patient is a high-grade mental defective. Her height is 5 ft. 0 in., her arm span 5 ft. 2 in., and her crown-to-pubis and pubis-to-sole measurements are 2 ft. 4 in. and 2 ft. 7 in. respectively. There is slight flexion deformity of the fingers of both hands. Her external sexual development is normal. Menstruation is said to have started at the age of 9, and at present she is menstruating regularly, although the possibility cannot be excluded that she may in the past have missed an occasional period.

Colour-vision and hormone-excretion studies together with palm-print analysis are being made and will be reported on later.

Nuclear Sex

Examination of buccal mucosal cells showed that the proportion of chromatin-positive cells was excessive, 41% having a single body and 48% double bodies. The blood polymorphs were those of a female, 11 "drumsticks" being found in 500 cells.

Chromosome Analysis

Peripheral blood and a sample of skin from the midline of the anterior chest wall were cultured. The chromosome counts are shown in table III.

In both tissues the modal number was 47, and deviations from this are considered to be mainly due to artefacts arising during the preparation of the cells. Analysis of the cells with 47 chromosomes showed a consistent pattern with an additional chromosome present in the size range in which the X is found. In view of this and the buccal smear findings the patient is considered to be a "super-female" with an XXX sex-chromosome constitution.

Comment

As far as is known this patient has no physical abnormality related to her XXX constitution. It is uncertain whether her mental defect is incidental or is causally related to her chromosome constitution. She appears at present to menstruate regularly, and studies are being made to confirm that ovulation is occurring. She is, therefore, unlike the "super-female" previously reported who developed secondary amenorrhœa at the age of 17, and who also had had underdeveloped external genitalia prior to œstrogen therapy.

The findings in this patient raise the possibility that some women with an XXX constitution are fertile. If this is the case they will produce oocytes with X and XX sex chromosomes, and their progeny would therefore be expected to include individuals with an XXX and an XXY constitution. In consequence examination of the parents of persons found to carry an abnormality of the sex chromosomes is desirable. Some patients with other types

TABLE IV—KARYOTYPE ABNORMALITIES, WHICH MAY BE ASSOCIATED WITH AMENORRHŒA

Chromosome count	Sex-chromosome complement	Sex chromatin		Clinical syndrome	References
		Buccal smear	Polymorphs		
45	XO	Negative	Negative	Turner's syndrome	(a) Ford et al 1959a (b) Jacobs and Keay 1959
45/46	XO/XX	Positive (? weakly) or negative	?	Turner's syndrome	Ford 1959
46	XY	Negative	Negative	(a) Testicular feminisation (b) Pure gonadal dysgenesis	(a) Jacobs et al 1959c (b) Harnden and Stewart 1959
46	X—partially deleted X	Weakly positive	Negative	Primary amenorrhœa	This communication
47	XXX	Positive with double chromatin bodies	Positive	"Super-female"	(a) Jacobs et al 1959a (b) This communication
47/45	XXX/XO	Positive with double chromatin bodies	Negative	"Super-female"/Turner syndrome mosaic	This communication

of sex-chromosome abnormality may also be fertile If this is so the secondary non-disjunction which must occur may be an important additional cause of karyotype abnormalities involving the sex chromosomes

Discussion

The data in this report, together with previously published data, show that seven types of aberration of the sex chromosomes can be associated with amenorrhœa (table IV) Apparently such aberrations are not inevitably accompanied by amenorrhœa—in one case of Turner's syndrome with an XO constitution the patient menstruated regularly for six years (Stewart 1960), and in both patients with an XXX constitution menstruation began, ceasing in one after two to three years and continuing in the other at the age of 21 The information in table IV is of necessity limited, but at this early stage of development of our knowledge it may be of some value to those investigating patients with persistent amenorrhœa

There are good grounds for advocating routine examination for sex chromatin in buccal mucosal smears in all cases of amenorrhœa for which no satisfactory cause is found If cells with double chromatin bodies are found, as well as cells with single bodies, it is likely that some or all of the patient's body cells contain more than two X chromosomes, and that she may be either a "super-female" or a mosaic with one stem-line containing three X chromosomes, or she may have an even greater number of X chromosomes More than three X chromosomes are theoretically possible, but, as the precise relationship between the number of X chromosomes and the number of chromatin bodies is not understood, the findings in the buccal smear cannot be predicted

If examination of the buccal smear in a phenotypic female shows no chromatin bodies, then the patient may have either an XO or an XY constitution Presumably an individual who is an XO/XX mosaic may show no chromatin bodies or, according to the degree of admixture of the two stem-lines, may show anything up to the normal number of such bodies Similarly it is possible that individuals with a partial deletion of one X chromosome may show either a normal number of cells with chromatin bodies in the buccal smear or an equivocal number, or possibly none at all according to the extent of the deletion Furthermore the data on case 2 suggest that if the deletion is between certain limiting sizes the chromatin bodies will appear unusually small

Quite apart from their intrinsic clinical interest the data presented in this report raise more fundamental biological considerations—in particular the importance of mosaicism in human pathology and the possible genetical information to be obtained from the study of persons with partial deletions of one chromosome

Summary

Data are presented on a phenotypic female who is presumed to be an XXX/XO mosaic—i e, she has two stem-lines of cells in her body containing 47 and 45 chromosomes with sex constitutions of XXX and XO respectively

A phenotypic female who is presumed to have a partial deletion of one X chromosome is described

A "super-female" who is menstruating regularly is described

We are indebted to Miss K Buckton for chromosome measurements, and to Miss I Tough for some of the chromosome counts, to Dr W M Harrowes and the nursing staff of St Joseph's Institution, and also to Dr E J Gilmore, to Dr Eric Samuel, Dr G T Loughborough, and Dr F Cosin, who kindly gave advice on X-ray interpretation, and to Miss M Brunton, Miss S Brunton, Mr A Ross, and Miss G Woodcock for technical assistance

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INTRAHEPATIC TYPHOID INFECTION

AS CAUSE OF THE CARRIER STATE

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Salmonella typhi may dwell for many years in the gallbladder, and living bacilli may be eliminated through the bile and excreted in the fæces, thereby creating an intractable carrier state Thus Botsford (1941) reported a case in which living bacilli were found in the fæces and gallbladder 43 years after the primary infection But removal of a gallbladder containing living bacilli does not always eradicate them Topley and Wilson's textbook says

> " a high proportion of both typhoid and paratyphoid carriers can be freed from their infection by cholecystectomy
>
> In the occasional carrier, however, even removal of the gallbladder proves a failure, it is not yet clear in what part of the intestinal tract the focus of infection persists, though there is reason to believe that it is in the biliary passages of the liver" (Wilson and Miles 1955)

We have found no other recent reference to this latter localisation, but Askanazy (1928) mentioned a case of persistent excretion of typhoid bacilli after cholecystectomy, and concluded that the organisms had settled in the intrahepatic bileducts.

In four cases we have been able to confirm that the site of the chronic typhoid infection may be in the bileducts themselves, even in the absence of the gallbladder (case 3).

Case-records

THE FIRST CASE

Mrs A., aged 34, had had typhoid in 1942. During her illness she had gallbladder colic, and she was told that her liver was enlarged. The attacks later ceased and she maintained good health for 13 years.

At the end of 1954 she was troubled by general malaise, lack of appetite, nausea, and pains in the right upper abdomen and lower chest. She lost 10 kg. Icterus appeared a month before she came into this hospital on March 3, 1955. Her general condition was then fairly good. Slight jaundice, liver enlarged three fingerbreadths below the costal margin, blood-pressure 120/75 mm. Hg.

Erythrocyte-sedimentation rate (E.S.R.) (Westergren) 22 mm. in the first hour, Hb 10 g. per 100 ml., leucocytes, 4600 per c.mm. (polymorphs 45%, eosinophils 4%, monocytes 6%, lymphocytes 45%), serum-bilirubin 8 mg. per 100 ml., liver-function tests normal, stool culture, *S. paratyphi B*, Widal test positive to *S. paratyphi B* at a titre of 1/200. A cholecystogram made with a double dose of 'Telepaque' (iopanoic acid) did not show the gallbladder.

After treatment with chloramphenicol for 23 days, the gallbladder was removed (it contained four stones). The cystic duct was tied close to the common bileduct which was somewhat enlarged and contained pale bile but no stones. A T-tube was left in place. Bile taken from the gallbladder and common bileduct at operation gave a good growth of *S. paratyphi B*. Washing of the T-tube with oxytetracycline solution was begun immediately. Cultures of fæces and of bile from the T-tube remained positive until the 27th day after operation, after which they were consistently negative. Cholangiography through the T-tube on the 11th postoperative day showed normal bileducts, no stones, and free passage into the duodenum. The drain was removed 6 weeks after operation.

The patient has since been in good health, and fæcal cultures have remained negative.

THE SECOND CASE

Mrs B., aged 45, had had typhoid in 1939 in a concentration camp. After recovery she had no complaints until a year before admission to this hospital on March 7, 1958, when she had frequent attacks of what was thought to be gallstone colic.

For 2 days she had had severe pain in the right hypochondrium, vomiting, and fever. There was tenderness and guarding in the right hypochondrium, and slight jaundice. Leucocytes, 9500 per c.mm., urine, bilirubin positive.

Operation revealed a small, contracted, and thick-walled gallbladder containing three small stones. The common bileduct was somewhat enlarged and contained purulent bile, but there were no stones, and passage into the duodenum was free. Bile culture was positive for *S. typhi*. The gallbladder was removed and a T-tube left in the common bileduct.

The gallbladder showed chronic unspecific inflammation, mostly in the submucosa, with an obliterated cystic duct. The T-tube was irrigated first with chloramphenicol and later with oxytetracycline. Cholangiography through the tube 2 weeks after operation showed normal hepatic ducts, free passage into the duodenum, and no calculi. About 7 weeks after operation, cultures from bile and fæces became sterile.

THE THIRD CASE

Mrs C., aged 44, was admitted on Feb. 4, 1958. She had had cholecystectomy in 1942 for cholelithiasis, and typhoid 6 years later. In 1953 *S. typhi* was found in the fæces, and cultures remained positive despite treatment. In 1955 she had pains in the right hypochondrium, with fever and jaundice, each attack lasting 3–4 weeks, and in 1957 she had recurrent jaundice with fever. Laboratory findings in these attacks were bilirubin 1·5–7 mg. per 100 ml., serum alkaline phosphatase up to 17 Bodansky units, serum-cholesterol, 350 mg. per 100 ml., liver-function tests normal, leucocytes, 8000 per c.mm., E.S.R. 86 mm. in the first hour. Intravenous cholangiography showed enlargement of the hepatic ducts and a relatively narrow common bileduct.

She was admitted with pains, jaundice, and fever. The fæces contained *S. typhi*.

A week later, the common bileduct was explored. It contained many soft calculi, and the enlarged hepatic ducts were stuffed with countless soft stones. Bile culture was positive for *S. typhi*. The common bileduct was afterwards irrigated with oxytetracycline through a T-tube. Cholangiography 2 weeks after the operation showed normal hepatic and extrahepatic ducts, and no stones or obstruction.

Cultures of bile and fæces did not become negative until 10 weeks after operation. The drain was removed 3 months after operation.

THE FOURTH CASE

Mrs D., aged 45, was admitted in August, 1955. In 1941 she had typhoid in a German concentration camp. A year later, she had jaundice for 2 months without pains or fever. In 1954 she had jaundice with fever, chills, and pains in her right hypochondrium radiating to the back, and subsequently she had similar attacks almost every 2 months.

On admission, the liver and spleen were 5 cm. below the costal margin. Laboratory findings: E.S.R. 122 mm. in the first hour, Hb 11·2 g. per 100 ml., leucocytes, 1800 per c.mm. (differential count normal), thrombocytes 75,000 per c.mm., blood-urea, 22 mg. per 100 ml., serum-proteins, 8·1 mg. per 100 ml. (albumin 4·5 mg., globulin 3·6 mg.), thymol turbidity test negative, Takata-Ara negative, serum-bilirubin, 12 mg. per 100 ml., serum alkaline phosphatase, 31·5 Bodansky units, prothrombin, 117%, serum-iron 200 mg. per 100 ml. In the urine, urobilin and bilirubin were increased. The fæces contained bile pigments.

A tentative diagnosis of biliary cirrhosis with attacks of cholangitis and hypersplenism was made.

In October, 1955, laparotomy was performed. A cirrhotic liver was revealed and greatly enlarged veins in the abdomen, the gallbladder was very small and contracted, and in the hilus of the liver huge varices, as big as the thumb, were found. Exploration of the common bileduct was practically impossible. The pressure in a mesenteric vein was 40 cm. water. Splenectomy was therefore undertaken, with an end-to-side splenorenal shunt. Recovery was uneventful and the blood-count became normal with Hb 10 g. per 100 ml., leucocytes 9200 per c.mm., and thrombocytes 470,000 per c.mm.

The œsophageal varices disappeared after the splenorenal shunt, but she continued to have attacks of jaundice with fever, serum-bilirubin above 5 mg. per 100 ml., and high alkaline phosphatase. Treatment with antibiotics did not prevent the attacks.

In April, 1956, another attempt was made to explore the common bileduct. The gallbladder was entered through the ampulla of Vater. Intraoperative cholangiography showed normal bileducts with no obstruction, but the gallbladder did not fill. The abdomen was closed without drainage of bileducts.

Liver biopsy at operation showed biliary cirrhosis. Culture of bile from deep in the hepatic ducts gave a rich growth of *S. typhi*. Despite large doses of chloramphenicol the fæces continued to grow *S. typhi*. The patient was therefore given a typhoid vaccine, containing up to 250 million organisms. For a time the fæcal cultures were negative, but bouts of fever with jaundice still occur. The serum alkaline phosphatase remains high (21–41 Bodansky units). Fæcal cultures are occasionally positive.

Comment

The four cases described prove that the focus of persistent typhoid infection in carriers may be in the liver itself, and not only in the gallbladder as is generally supposed Case 3 is especially significant because the patient had typhoid fever 6 years after removal of her gallbladder The persistent infection of the bileducts was probably the cause of the calculi, creating a vicious circle of stasis, infection, and stone formation

In all four cases bile from the hepatic ducts contained *S typhi*, and, in the three cases where the common bileduct was drained, excretion of *S typhi* in the bile continued for a time Another important finding is that in cases 1 and 2 jaundice must be attributed to typhoid cholangiolitis, since no obstruction of the bileducts was found

In three cases bile drainage through an indwelling T-tube was followed by disappearance of the bacilli from the bile and fæces, but this favourable result may have been partly due to irrigation of the bileducts Again the benefit of irrigation may have been due either to the antibiotic content of the fluid or to its mechanical action

Drainage may be also beneficial in lowering the intraductal pressure In the normal biliary tract this tends to remain at about 100 mm of water Normally the sphincter of Oddi is contracted in the fasting state and withstands a pressure of 100–150 mm of water (Doubilet and Colp 1937) In the presence of biliary infection, which may cause spasm, the pressure may increase to 250–300 mm of water or more (Doubilet and Colp 1937, Mallet-Guy et al 1947) This increase is avoided when free drainage of the biliary-passages is established Continuous siphonage through the T-tube brings the pressure down and keeps the extrahepatic biliary passages empty Thus the flow of bile from the liver has no extrahepatic resistance to overcome

The fourth case is of particular interest because of the biliary cirrhosis with portal hypertension which slowly developed after typhoid fever The cirrhosis remained very active for years and was complicated by attacks of cholangiolitis It is hard to say whether the typhoid bacilli which lingered in the deep biliary ducts were responsible for the cirrhosis, or whether the cirrhosis helped to maintain the infection within the liver In this case, treated without drainage or irrigations, the patient remained a typhoid carrier

How do the typhoid bacilli reach the bile-passages? During the illness the bacilli may enter the intrahepatic biliary passages from the blood-stream and thus infect the gallbladder, but it has been proved experimentally that they may reach the gallbladder directly from the blood-stream Under natural conditions entry may probably be by either route (Rous and Jones 1916) But the question remains why, in some cases, the bacilli continue to live happily in the liver even after the illness is over

A hypothesis proposed by Spink (1956) in his work on brucellosis may be helpful He supposes that for the annihilation of gram-positive organisms phagocytosis is essential but humoral antibodies are not On the other hand, gram-negative organisms, like brucellæ and salmonellæ, are killed mainly by the bacteriolytic effect of antibody plus complement, and phagocytosis is not very important Further, if the bacteria are able to live intracellularly, as brucellæ certainly can, they might even be *protected* against humoral antibodies and antibiotics by the phagocytic cell As far back as 1916 Rous and Jones demonstrated that typhoid bacilli in the leucocytes are protected against immune serum and the lethal action of cyanide, and Goodpasture (1937) proved that intracellular parasitism exists in typhoid Such a condition, therefore, might in some cases be responsible for the intrahepatic carrier state

Clearly, in the intrahepatic stage of chronic infection, cholecystectomy alone would be of no avail In every carrier in whom a cholecystectomy is performed the bileduct should be drained even if the choledochus appears normal and contains no calculi

Summary

In four typhoid carriers the common bileduct was explored because of symptoms of obstructive jaundice and cholangiolitis In two of them no obstruction was found, and the jaundice was attributed to typhoid cholangiolitis

In all four cases the bile from the deep biliary passages contained living typhoid bacilli

In three the common bileduct was drained and irrigated with antibiotics *Salmonella typhi* disappeared from the bile after 1 to 3 months Fæcal cultures have remained sterile for periods varying from 18 months to 4 years

The patient whose common bileduct was not drained still has bouts of fever and jaundice, and fæcal culture is still occasionally positive

Whenever cholecystectomy is performed for the carrier state, the common bileduct should be drained

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Addendum

Since the submission of this paper for publication, two additional cases of chronic intrahepatic *S typhi* infection have been treated successfully by bileduct drainage

NON-ESTERIFIED AND ESTERIFIED FATTY ACIDS IN HEPATOCELLULAR DISEASE

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The non-esterified fatty acids (N E F A) of plasma seem to be a major link in the transport of fatty acids from depots to liver and peripheral tissues (Gordon and Cherkes 1956) in the fasting state, the other possible sources of circulating N E F A being intravascular hydrolysis of plasma triglyceride (esterified fatty acids [E F A]) and lymph (Fredrickson and Gordon 1958) Since it has been shown experimentally that liver cells can take up N E F A directly from the blood at a high rate (Morris and French 1958, Roheim and Spitzer 1958), we decided to ascertain whether hepatocellular disease of different degree is associated with different N E F A levels To complete the picture the E F A was also studied

Material and Methods

The investigation was made on 12 normal adults (9 men and 3 women), 7 patients with compensated cirrhosis, 6 patients with decompensated cirrhosis, and 6 patients with severe, acute, fulminant hepatitis

The blood was drawn, whenever possible, in the postabsorptive state, and the sera were analysed on the same day The N E F.A were determined by the method of Davis (1947)

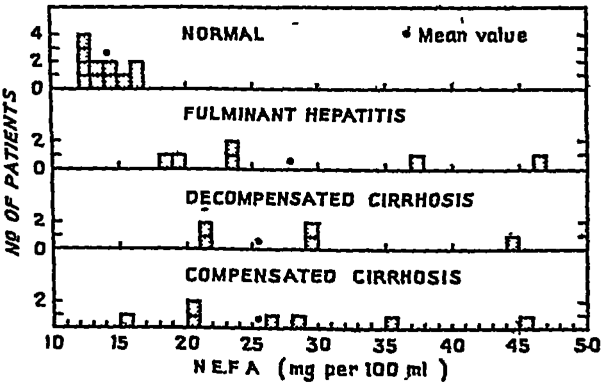
1 *Extraction* —The serum sample (3 ml) was added to 0 3 ml 0 2 *M* phosphate buffer at pH 6 0 and 1 5 ml of a 5% sodium dodecyl sulphate ('Duponol C') solution After saturation with sodium sulphate crystals, the mixture was extracted four times with 3 ml of ether, using a glass plunger for gentle mixing The ether phase was separated by centrifugation for ten minutes The solvent of the combined ether extracts was evaporated in a warm water-bath

2 *Titration* —The residue of the ether extract was dissolved in 2 ml ethanol and titrated with aqueous 0 01 *N* sodium hydroxide in a nitrogen atmosphere, using 1% thymol-blue in ethanol as indicator The end-point was to a light green In the blank experiments 2 ml ethanol replaced the serum

3 *Calculation* —NaOH (unknown—blank) × 94 = mg of N E F A per 100 ml (expressed as oleic acid) or

$$\frac{\mu\text{g per litre}}{282} = \mu\text{Eq per litre}$$

4 *Recovery experiments* —Oleic acid added to human sera resulted in an average recovery of 98%, and a mixture of two different sera with previously known amounts of N E F A gave a difference of 4·7% between the theoretical amount and that actually obtained



N E.F.A in liver disease and in normal controls

To verify the possible influence of the esterified fatty acids in the method, triacetin was added to a known serum and it was not recovered because equal results were obtained with and without the added triglyceride

The E F A. were determined by Stern and Schapiro (1953) modification of the original method of Bauer and Hirsch (1949), using triolein as a standard

Results

The N E F A level of 12 fasting normal subjects averaged 14 21±1 38 mg per 100 ml (504±49 μEq per litre) (mean ± standard deviation) In 18 patients with liver diseases the average was significantly (P < 0 01) higher 27 93±8 86 mg (990 ± 314 μEq per litre)

When the patients were classified in relation to the severity of hepatocellular failure (see figure), the values in each group differed significantly (at 95% level) from those of the normal controls, but there were no significant differences between the groups The chart shows clearly that only one of the liver cases had normal N E F A values

The E F A values were controls, 313 66 ± 56 02 mg per 100 ml , patients with liver disease, 319 66 ± 53 67 mg. The difference was not statistically significant Nor did the values differ with the severity of the disease

Discussion

Selden and Westphal (1955) demonstrated that serum of rats treated with carbon tetrachloride contained significantly more N E F A than that of normal rats Stormont and Mackie (1959), measuring plasma-N E F A (method of Dole 1956) in 17 alcoholic patients with cirrhosis, observed higher levels (898 μEq per litre ± 47 S E) than in 22 controls (768 μEq ± 42 S E) Still higher levels were observed in 13 cirrhotics with coma or hepatocellular failure (1269 μEq ± 126 S E)

Our findings resemble those of Stormont and Mackie (1959), with slightly higher average (28 0 mg pre 100 ml), in the more severe cases (fulminant hepatitis) (see figure)

The higher N E F A levels in liver disease could be due to increased peripheral production, to decreased oxidation or removal, or to both The first possibility can be dismissed because the E F A values did not differ significantly between normals and patients and because it is well known that diabetics who tend to have raised N E F.A levels (Bierman et al 1957a) also have high E F A levels (Hirsch et al 1953) The injection of insulin which—by inhibiting the release of fatty acids from tissue stores (Bierman et al 1957b)—causes a fall in plasma-N E F A also causes a fall in plasma-E F A Hence we deduce that the raised plasma-N E F A of patients with liver disease is due primarily to decreased oxidation or removal of N E F A The animal experiments of Morris and French (1958) and Roheim and Spizer (1958) support this view

The decrease in N E F A removal by the liver is associated with a decrease in cholesterol esterification (unpublished data) which we know to be impaired in hepatic diseases (Epstein and Greenspan 1936), although there was no absolute correlation between the rise in N E F A. levels and the fall in esterified cholesterol This is to be expected since Zieve (1953) has shown that the reduction in percentage of cholesterol esters is highly dependent on the degree of jaundice and somehow independent of the degree of hepatocellular damage

Summary and Conclusions

The levels of non-esterified fatty acids (N E F A) and esterified fatty acids (E F A) in the plasma were determined in 12 normal controls and 18 patients with liver disease

The level of N E F.A was significantly higher in liver disease than in the controls, but the E F A levels showed no such difference

The findings suggest that in liver disease the removal of N E F A from the plasma is impaired

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AN UNUSUAL FORM OF FAMILIAL OSTEODYSTROPHY

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IN 1956 there presented himself at a rheumatism clinic a patient described by his own doctor as suffering from "rheumatoid arthritis of the spine and hips"

For twenty years he had had some discomfort in both hips, but he had been able to carry on his work in a spinning-mill without interruption In fact he led an active life with tennis as his principal recreation Now at the age of 46 the pain had reached a stage where some relief was necessary His childhood history was not remarkable, and so far as he knew he had been normal in size until the age of 13 All his life he had had nocturnal enuresis

He was a man of normal intelligence who was remarkable for the smallness of his stature—some 4 ft 4 in in height The neck was short, and he had an exaggerated lumbar lordosis with complete fixation of the lumbar spine The muscular development was good but movement at both hip joints was much limited No other joints were affected There was no significant abnormality in the cardiovascular system or in the lungs, although the chest expansion was negligible (fig 1)

Skiagrams confirmed the presence of degenerative changes in the hips and showed unusual appearances in the spine which will be described below

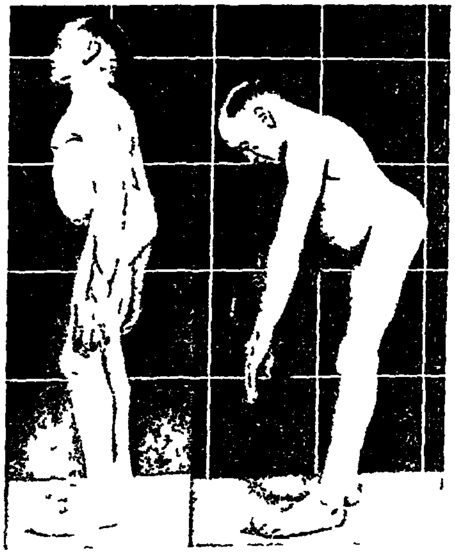

Fig 1—The propositus

The patient had 8 sibs (fig 2) 3 brothers also were of small stature, his remaining 3 brothers and his 2 sisters were of normal size, but one of the sisters had rheumatoid arthritis There was no consanguinity in the parents, who were of average stature

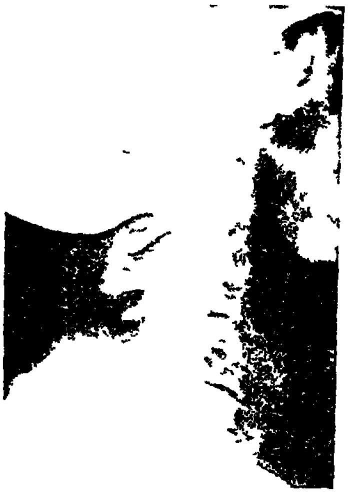

Fig 3

Fig 4

Fig 3—Propositus: cervical spine

Fig 4—Case C lumbodorsal spine showing fusion

The family proved most cooperative, and all the sibs and the children of 1 of the affected brothers were examined radiographically The propositus was unmarried, but 1 of the affected sibs has 2 children and another has 11 children, all of whom appear to be developing normally

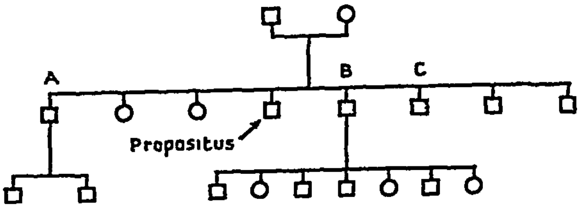

Fig 2—Family tree

The other affected members of the family were as follows

A, aged 54 Always healthy, in thirty years has had ten weeks off work On direct questioning he admitted to some twinges of pain in the upper lumbar region He was 4 ft. 8 in. in height and of average muscular development Chest expansion $^{1}/_{2}$ in No abnormality in the lungs, cardiovascular system, abdomen, or central nervous system The cervical spine had about 50% of the normal range, and the lumbar spine was fixed No abnormality in other joints

B, aged 42 Quite fit apart from occasional pain in the right groin No discomfort in back He was 4ft 4 in in height and well built proportionately Chest expansion 1 in No abnormal physical signs in the lungs, cardiovascular system, abdomen, or central nervous system The cervical spine had about 75% of the normal range, and the lumbar spine was fixed Movement at the right hip-joint was much restricted, but the remaining joints were normal

C, aged 39 Admitted to periodic pain in both shoulders but was otherwise fit and, like the propositus, a keen tennis-player His height was 4 ft 6 in with a chest expansion of $^{1}/_{2}$ in There was nothing of note in the lungs, cardiovascular system, abdomen, or central nervous system Movement of the lumbar spine was somewhat limited, but the cervical spine had a normal range Remaining joints were normal

The radiographic appearances were similar, though they varied in degree between the four affected members

Cervical spine—The body of the 2nd cervical vertebra is almost double the height of the remaining cervical vertebræ with an unusually prominent spinous process The other bodies are flattened, with narrowing and irregularity of the intervertebral spaces The bone structure appears normal (fig 3)

Dorsal spine—Flattening of the bodies with narrowing and irregularity of the intervertebral spaces Calcification is taking place in the discs In the case of the propositus the dorsal and lumbar spines have fused with obliteration of the intervertebral spaces The costovertebral joints are irregular Bone structure is maintained (figs 4–8)

Lumbar spine—Flattening of the bodies with osteophyte formation The intervertebral spaces vary from advanced narrowing and irregularity to complete obliteration In the

Fig 5

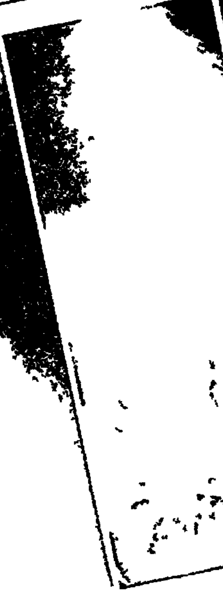

Fig 6

Fig 7

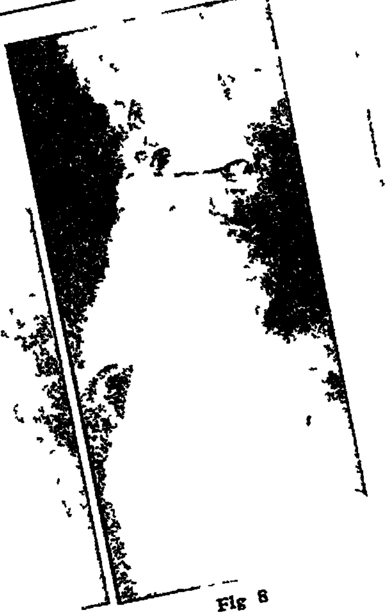

Fig 8

Fig 5—Case C lumbar spine showing fusion and " cod-fish-mouth " appearance

Fig 6—Propositus lumbodorsal spine showing fusion

Fig 7—Propositus lumbar spine showing fusion

Fig 8—Case B lumbar spine showing " cod-fish-mouth " appearance

lower lumbar region the anterior third of the bodies has been eroded, giving the appearance of an open cod-fish mouth (fig 8) This appearance is quite characteristic in all the cases The interfacetal joints show a tendency to fuse. The bone structure appears normal

Pelvis —This is small with a tendency towards protrusion of the acetabula

Hip-joints —In 2 cases there is flattening of the femoral heads with narrowing of the joint space The appearances are those of osteoarthrosis

Hands and feet —Normal

Examination of unaffected members of the family showed no abnormality

Discussion

The appearance in these cases corresponds to the form of dwarfism classified by Fairbank (1951) as the short-trunk long-limb type In this group are included the Morquio-Brailsford syndrome, gargoylism, spinal caries, and severe scoliosis The last three may be excluded, but the condition might be a *forme fruste* of Morquio-Brailsford syndrome.

In his original report Brailsford (1929) described the case of a boy aged 3 years in whom the abnormality was first noted at the age of 13 months when he began walking The radiographic appearances included irregularity and fragmentation of the epiphyses, irregular size and shape of the vertebral bodies, and dislocation of the lumbodorsal vertebræ In addition there was pointing of the bases of the metacarpals About the same time Morquio (1929) reported a familial condition in which there was consanguinity of the parents 4 of their 5 children showed appearances characterised by bone changes without pain affecting the whole of the skeleton except the head 8 cases ascribed to disordered epiphyseal development were described by Ruggles (1931) The early signs were apparent at the age of 2-3 months, but in some cases were overlooked until the child began to walk Like Morquio he noted hypermobility of the joints Gross and widespread deformities were present in cases reported by Ellman (1933, 1949) and Fairbank (1947), while Toma (1953) stated categorically that in true osteochondrodystrophy defective ossification of the whole skeleton was always present Recently Lomas and Boyle (1959) have suggested that an X-ray of the hands should be used as a screening test since shortening of the 4th and 5th metacarpals seem to be characteristic

In the present cases the spine and hips are the only parts affected, and the spine shows a remarkable fusion The hands are not affected, nor are the knee-joints abnormal The onset seems not to have occurred until shortly before puberty As there was doubt regarding the diagnosis the help of Dr J F Brailsford was sought He kindly examined the skiagrams and expressed the opinion that the condition is not osteochondrodystrophy but a familial disorder not hitherto described

Summary

A familial condition of dwarfism is reported in which fusion of the dorsolumbar spine is associated with degenerative changes in the hip-joints

I wish to thank Dr D M Coates for his assistance with the radiology of the family, Mr L. Firth, radiographer, Mr G R Dixon for clinical photographs at the Devonshire Royal Hospital, Buxton, and the clinical photography department of Withington Hospital for the reproductions of the skiagrams

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" I see in a medical school not a trade school where technicians pass on mechanically and by ritual the craft and craftiness of those who know the ropes Certainly we must impart what we can of the art of medicine, its central spirit, but no lecture or course can teach it, no audio-visual mechanism can transmit it, no department of general practice or of anything else is its proper or only custodian It moves unseen along unmeasured ways, it is acquired unconsciously, by association, by subtle forces almost beyond the reach of analysis and outside the realm of synthesis "—W B BEAN, *Northw Med* 1959, 58, 535

CEREBELLAR ATAXIA FOLLOWING CHICKENPOX

S Levin
M B W'srand, M R C P E, D C H
OF JOHANNESBURG

> "They reel to and fro and stagger like a drunken man"
> *Psalm* 107 27

When Europe awakened from the slumber of a thousand years, Medicine also roused itself from the torpor induced by the dead hand of Galen Diseases came to be named—among them the four types of Pox the Great Pox (syphilis), Small Pox, Cow Pox, and Chicken Pox, so called because the bird typified something gentle, mild, and fragile The term "chicken-hearted" has the same origin Of late, however, evidence has accumulated that chickenpox may occasionally be anything but a gentle or mild infection Viral encephalitis is much in the medical news—so much so that the impression may be gained that varicella encephalitis is not unusual Far from it, chickenpox encephalitis is in truth a *rara avis*, and when the cerebellum is primarily affected it is doubly rare

Case-record

Oct 8, 1959—A healthy 7-year-old lad developed mild chickenpox He stayed in bed a few days, having no treatment whatever—not even aspirin

Oct 15—In the evening he complained of headache and vomited three times

Oct 16—Vomited in early morning, no further headache; vaguely mentioned giddiness

He did not appear unduly ill Temperature 99°F, pulse-rate 90 Mentally he was befogged, it took some time before questions put to him penetrated He answered slowly, haltingly, monotonously, and with not much sense at that He had a constant fatuous smile on his face

The neck was slightly stiff, no Kernig's sign, cranial nerves normal, no nystagmus, gag reflex present He could not sit up, trunk ataxia being obvious When he was propped up, the tripod sign was present Abdominal reflexes normal The limbs were rather hypotonic, tendon reflexes present but not brisk No obvious impairment of sense of touch, position, or pain Plantar reflexes flexor, sphincters unaffected There was severe ataxia of both arms and legs The finger-nose test was very poorly performed, both with eyes open and closed There was much intention tremor He was even worse with the heel-knee-shin test He could not stand alone, being equally unsteady with eyes open or closed He could stagger across the floor if supported by both arms He was utterly hopeless at the dysdiodokinesis test A lumbar puncture was not done, being considered unnecessary

Oct 19—Had vomited daily, but had no headache There was no fever, no neck rigidity, no nystagmus, no sensory disturbances He was brighter, mentally more clear, but still had an irritatingly silly grin Speech was no longer so painfully laboured, but still decidedly slurred He replied more rapidly to questions He could sit up unsupported, but was still grossly ataxic in arms and legs Dysdiodokinesis severe Wildly unsteady on his legs, needed constant support, and very anxious to get back into bed

Oct 22—Mind clearer, brighter, had lost his fatuous grin Eating well, eager to play, wanted to get out of bed Speech sharper, taking an interest in drawing, but having difficulty with the crayons because of his hand ataxia Finger-nose test and heel-knee test improved, but still ataxic, and needed physical assistance while stumbling across the floor No sphincter difficulties No vomiting in the past three days

Oct 23—Took one step alone without support

Oct 24—Managed to lurch across a room unassisted Ataxia clearly displayed, speech slightly stilted Stood still without falling—with eyes closed Mentally clear

Oct 29—Parents complained that patient was too subdued, his memory poor, his speech stilted and babyish To me, speech seemed normal Vision and hearing apparently normal Dysdiodokinesis present, legs and arms slightly ataxic, but could draw a circle and a triangle Still shaky on legs, with a drunken gait, could not get up quickly from the floor, could not run

In the meantime both the sister and the father had recovered from chickenpox (moderately severe in father's case) and had no subsequent complications

Nov 2—To all intents and purposes fully recovered

Discussion

In cases of varicella severe enough to be admitted to hospital, the incidence of encephalitis is 1 in about 400–500 (Bullowa and Wishik 1935, Appelbaum et al 1953) Recent estimations suggest that in the general population encephalitis complicates chickenpox in 1 case in about 6000–10,000 (Meade 1959)

Assuming that nearly all children have had chickenpox at 15 years, then roughly 1 in 15 of them will develop varicella annually This 0–15-year age-group accounts for perhaps 20% of the total population in Western society, so in any population of a million, about 200,000 are children up to 15 years If 1 in 15 of them gets varicella annually, then some 15,000 will be affected If we assume an incidence of encephalitis of the order of even 1 in 5000, then there will be 3 children annually with encephalitis in any population of 1,000,000 The cerebellar form of encephalitis occurs in about a third of cases, so every year perhaps 1 child in a million population (and probably more than a million) will get cerebellar ataxia following chickenpox

Many of the reports of chickenpox encephalitis in the past fifteen years have come from Australia (Swan 1946, Camens 1950, Southcott 1953, Lander 1955, Nicolaides 1957)

Clinically, chickenpox encephalitis does not differ from other forms of viral encephalitis The cerebrospinal fluid usually has less than 100 lymphocytes (occasional polymorphs) per c mm, and may in fact be quite normal (Appelbaum et al 1953) Peripheral neuritis, especially sensory neuropathies, may occur (Heywood and Richardson 1956, Simon et al 1957) In about a third (Appelbaum et al 1953) or perhaps a quarter (Underwood 1935) of the cases the picture is one of cerebellar affection, though the complete cerebellar syndrome is seldom present—nystagmus, for example, being infrequent (Underwood 1935) In favourable cases the abnormal symptoms and signs clear for the most part within a week or two

The mortality rate of chickenpox encephalitis is about 5% (Appelbaum et al 1953) to 10% (Meade 1959), and some 15% are left with permanent neuropsychiatric handicaps, such as retardation, palsies or blindness A very small proportion of the handicapped group may recover after months or years, while a very small proportion of those apparently fully recovered will develop some neuropsychiatric sequel after months or years (Meade 1959)

There is no correlation between the severity of the encephalitis or the cerebrospinal fluid findings and the ultimate prognosis, but convulsions or concomitant pneumonia are unfavourable signs The time of onset of encephalitis in relation to the onset of the rash is also of no prognostic import, the encephalitis usually develops three to eight days later, but may develop at the same time or as much as three weeks later

Although in one reported case a patient recovered while being treated with cortisone (Henderson 1953), this substance increases the severity of varicella and may be responsible for death. A real problem arises in hospitals where children with rheumatic fever are being treated with steroids should varicella break out in the ward, the results may be catastrophic (Haggerty and Eley 1956, *Journal of Pediatrics* 1957)

Varicella is a generalised infection Postmortem studies have shown necrotic lesions and intranuclear inclusion bodies in virtually every organ and tissue of the body (Librach 1959, Downie 1959) Second infections of chickenpox take a neurotropic form—zoster, which is a varicella infection in those with a partial immunity (Librach 1959) It is thus odd that overt neurological complications are so rare with chickenpox (Pathy 1955)

My thanks are due to Dr S Jacobson, who confirmed the diagnosis

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Preliminary Communications

CHRONIC PANCREATIC DISEASE AND PROTEIN MALNUTRITION

STRIKING changes are seen in the pancreas in children who have died of protein malnutrition, and there is also considerable clinical and experimental evidence that protein deficiency can produce pancreatic lesions Yet from those areas most noted for a very low dietary intake of protein and for a high incidence of kwashiorkor reports of pancreatic disorders in adults are infrequent In this communication I should like to draw attention to a chronic pancreatic disorder with atrophy, fibrosis, and calculus formation as seen in twenty young adult Africans Pancreatic atrophy and fibrosis is often found at necropsy, and many patients with steatorrhœa and clinical manifestations of a malabsorption syndrome are probably in the earlier stages of a pancreatic disorder which will later cause calcification

The records of Mulago Hospital, over the 7-year period before the first case was diagnosed clinically in 1958, reveal four cases of pancreatic calculi in some 3500 necropsies (0 1%), and four cases diagnosed clinically or at operation as chronic pancreatitis Two of these patients were recently traced and found to have pancreatic calcification. During one year all patients attending the diabetic clinic were examined radiographically, and pancreatic calcification was noted in 8% Only two of nine patients with steatorrhœa had pancreatic calcification. Some three hundred pancreases collected from consecutive necropsies at Mulago Hospital were also examined radiographically Calculi were noted on preliminary palpation and section in two, one of which had been diagnosed in life, but the remainder showed no calcification Finally all X-ray films of the upper abdomen taken in the previous 5 years were reviewed , but in the X-rays of some 3500 people calcification was not demonstrated

CLINICAL FEATURES

Of the twenty cases I have seen, five were found incidentally at necropsy, ten patients were attending the diabetic clinic, two had severe malabsorption syndromes, and three presented with chronic upper-abdominal pain

Fourteen were males, and six were females The age at onset of symptoms ranged from 10 to 50 years, the average age being 29 in each sex. Fourteen patients were from the Ganda tribe, which forms the indigenous population around Kampala, and whose members are for the most part peasant farmers The others were immigrants from nearby Ruanda-Urundi, and were mostly poor unskilled labourers The diet of the Ganda is far better than that of the immigrants, but both have a low-protein, low-fat, high-carbohydrate intake [1]

The possibility of alcoholism was explored in sixteen cases, and four gave a history suggesting a large intake of local beer and spirits, but none could be regarded as a chronic alcoholic None showed evidence of gallbladder disease in the form of cholecystitis or calculi

Thirteen patients were much underweight and poorly nourished, four of them had parotid-gland enlargement and six had significant changes in the colour and texture of their hair The remaining patients appeared well nourished although it was not possible to exclude a previous nutritional deficiency

Thirteen of the eighteen patients who gave an adequate history had pain, and this was usually moderately severe, recurrent, upper abdominal pain, most patients did not volunteer a complaint of pain, which emerged only on close questioning This suggests that there were no attacks of acute hæmorrhagic pancreatitis

INVESTIGATIONS

The radiographic appearances varied from fine disseminated calculi in the tail and body of the pancreas to larger discrete calculi which, in some cases, were so diffuse as to completely outline the pancreas Several patients with very gross calculi (see figure) had never had any abdominal pain

Glucose-tolerance tests were performed on fifteen patients, and they were diabetic in twelve In the other three the curve was abnormal but not frankly diabetic, suggesting that intestinal absorption was normal but that endocrine secretion was unable to meet the normal carbohydrate stress

A tendency to hypoglycæmia, after insulin therapy was

Diffuse pancreatic calcification in a young adult African with diabetes mellitus but no significant history of abdominal pain noted in six of the twelve diabetics Five had peripheral neuropathy, and one man aged 20 had bilateral cataracts One patient was stabilised on tolbutamide, and the others required an average dose of 65 units insulin daily without major dietary control Ketosis was definitely present in four, was very mild on occasions in two, and absent in four others This pattern of behaviour is often seen locally in diabetics without pancreatic calcification, except for the greater tendency to hypoglycæmia and the somewhat larger insulin requirement [2]

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The serum-albumin level was below 3 5 g per 100 ml in fourteen of sixteen subjects Serum-cholesterol levels ranged from 80 to 180 mg per 100 ml, with a mean of 128 mg, as compared with 166 mg for healthy young adult East Africans [1] In fourteen patients the serum-amylase was raised on one occasion in one patient

HISTOLOGY

Material was examined from seven cases All showed various degrees of fibrosis In the earlier stages this seemed to be perilobular and periductal, and in the more advanced stages interacinar fibrosis had led to obliteration of the lobule In all cases pancreatic acinar tissue had nearly disappeared, although residual islands of tissue could always be seen Fatty infiltration or replacement was well defined in three cases Chronic inflammation was slight or absent The islets of Langerhans were usually hard to find and showed various changes—mainly of hypertrophy, hydropic degeneration, and fibrosis Calcification was seen only in duct spaces, and several cases had eosinophilic granular material in the acini or larger ducts The acini and ducts were dilated in all cases, giving a cystic appearance to many sections

DISCUSSION

The role of pancreatitis in the ætiology of pancreatic calcification seems to be well established, but it is difficult to relate all examples of pancreatic calcification to previous attacks of pancreatitis "Painless chronic pancreatitis" is a recognised term in the United States for patients with calcification but without history or symptoms suggestive of pancreatitis While previous pancreatitis may be a reasonable explanation in an area where the condition is common, it seems unwise to adopt generally a term which has such strong ætiological connotations Neither alcoholism nor biliary-tract disease appear important in the patients seen in Uganda

In considering protein malnutrition as a cause of pancreatic damage one must remember the striking changes seen in the pancreas in kwashiorkor [3] The particular vulnerability of the pancreas can probably be explained by the great turnover of protein within it In African adults with severe protein-malnutrition syndromes [4] the pancreas is small, atrophic, and fibrosed, the histological picture being dominated by atrophy and fibrosis without much cellular infiltration

Zuidema [5] described a series of eighteen young Indonesians with diffuse pancreatic calcification seen over 5 years Sixteen were diabetic, all were more or less emaciated, none had a history to suggest pancreatitis or alcoholism, and all had a very low protein intake Some had parotid-gland enlargement and/or hair changes, and Zuidema thought the severe pancreatic lesions were the end-result of long-continued protein malnutrition Twenty-seven others had a similar clinical picture without calcification, and Zuidema assumed that these patients had pancreatic fibrosis without calcification

Protein malnutrition is most easily recognised clinically when there is a relatively high caloric intake from starchy foods with insufficient protein intake [6] Possibly the high-carbohydrate diet usually eaten under the circumstances of protein deficiency leads to increased demands for enzymes and thus potentiates the effect of the initial low-protein diet [7]

CONCLUSION

Long-continued malnutrition may well lead initially to functional, but later to structural, changes in the pancreas of adults

To assess the relation of pancreatic damage in childhood to a possible increased susceptibility to protein deprivation in adult life is difficult, but one need not assume that this is a prerequisite for pancreatic damage in adults The additional or aggravating factors which determine why some, and not others, on low-protein diets develop pancreatic damage may be hookworm infestation, malaria, or intercurrent illnesses such as tuberculosis, cirrhosis, or chronic renal disease Almost certainly patients with pancreatic fibrosis and atrophy without calcification have the same basic condition as *those with calculi, calcification being the result, and not* the cause, of a chronic pancreatic disorder

I am grateful to Prof J N P Davies for his constant encouragement and for the use of the facilities of the department of pathology, to Dr G M Davies for radiological assistance and advice, and to Dr G T O'Conor for comment on the pancreatic histology

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VARIATION OF RESPONSE IN EARLY LIFE TO VACCINATION WITH LIVING ATTENUATED POLIOVIRUS AND LACK OF IMMUNOLOGIC TOLERANCE

INVESTIGATIONS conducted since 1955 have established that infants can be successfully immunised against poliomyelitis by the oral administration of living attenuated poliovirus [8–10] Analysis of these studies indicated that although infants more than 2 months old can be readily immunised with oral poliomyelitis vaccines, infants less than 2 months old appear to be relatively resistant to intestinal infection with the attenuated viruses

The immunological response of newborn infants to antigens such as diphtheria and tetanus toxoids is known to be either incomplete or non-existent [11 12], thus the ability of such infants to form antibodies in response to vaccination with attenuated live poliovirus warranted investigation More recently, our studies on susceptibility to intestinal infection with attenuated poliovirus in early life have been extended to include premature infants Preliminary findings in this group are also reported here

The living attenuated virus was also fed a second time to several groups of infants—in particular to those that had not responded by forming antibodies after the initial feeding during the first days of life This aspect of the study was designed to discover whether immunological tolerance had been induced—that is, whether in such infants there would be failure to produce antibodies after re-exposure to the same antigen later in life

METHODS

Forty-seven premature infants ranging in weight from 985 to 2220 g were given 5 7 log tissue-culture infective doses,,

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TABLE I—VARIATION OF INTESTINAL INFECTION AND ANTIBODY RESPONSE ACCORDING TO AGE

Age of infants (days)	Proportion of infants that excreted poliovirus in fæces		Proportion of infected infants with antibody response ‡	
	No *	(%)	No †	(%)
Premature				
3	44 47	94	14 25	56
Term				
<5	21 24	88	10 18	56
5 to <30	63 81	78	37 44	84
30 to <60	57 81	70	45 48	94
60 to 180	87 98§	89	66 69	96

* Numerator, number with virus in fæces, denominator, total with and without virus ($\chi^2 = 16{\cdot}66$, $P < 0{\cdot}01$)

† Numerator, number with antibody response to intestinal infection, denominator, total with and without response ($\chi^2 = 35\ 23$, $P < 0{\cdot}01$)

‡ All infants excreted poliovirus in fæces

§ Failure to excrete P-712 virus accounted for 7 of the 11 failures

(T C.I D $_{50}$) CHAT, type 1, attenuated poliovirus[13] by gavage on the 3rd day of life One hundred and forty-nine full-term infants were vaccinated by feeding three types of living virus in succession at 4-week intervals The CHAT (type 1), the P-712 (type 2),[14] and the W-Fox (type 3)[13] strains were used. The infants were from 1 day to 180 days old Most of them received from 5 0 to 5 7 log T C I D $_{50}$ of virus, each strain given separately in an ounce of milk

Fæcal specimens collected from the infants twice weekly were tested for cytopathogenic effect in tissue-culture consisting of explants of fresh monkey-kidney epithelium Viruses isolated from the fæces were identified by serum-neutralisation tests[15] The detection of poliovirus in the fæces on three or more occasions up to 28 days after vaccination was considered indicative of intestinal infection

Blood collected from the umbilical cord before vaccination and blood samples obtained at monthly intervals after vaccination from the same infants were submitted to a neutralisation test against the type of virus administered The metabolic inhibition test[16] and a modification of the more sensitive immune-inactivation test[17] were employed.

Persistent antibody levels of 1/8 or higher in sera collected after vaccination were considered to be evidence of a positive response to vaccination in infants whose cord blood had had no antibodies at a dilution of less than 1/8 Responses were judged significant in infants who had congenitally acquired poliomyelitis antibodies in their cord blood if the antibody titre after vaccination was at least 4 times greater than that expected after allowance for the normal decline of maternal antibodies[9]

The same amount of the same strain of virus was given orally a second time to infants 3–6 months after the first feeding

RESULTS

None of the premature and full-term infants given the attenuated viruses showed signs of illness There was no evidence of transmission of virus to other infants in the nurseries

Table I shows the proportion of infants in each age group in whom an intestinal infection developed, the proportion of infants who both excreted virus and had an antibody response is also shown No distinction was made among the results obtained with the three strains of virus because, except for a somewhat disproportionate number of failures of infection with P-712 in the group 60 days and older, the results were comparable Most readily infected were the premature infants, the full-term infants less than 5 days old, and those more than 60 days old, there appeared to be little difference among these groups In contrast, the proportion of infants between 5 and 60 days of age that excreted poliovirus in the fæces was relatively low

The percentage of infants who had a detectable antibody response was lowest (56%) in premature infants and in full-term infants less than 5 days old There was a definite increase in the percentage of infants (84%) that had an antibody response in the 5–30-day age-group 96% of the infants more than 60 days of age who became infected with virus had serological evidence of active immunisation (table I)

The same strains of virus were administered a second time to three groups of infants (1) those who had not been infected after the first vaccination and had not had an antibody response, (2) those who had been infected but had failed to show an antibody response, and (3) those who had been infected and had had an antibody response (table II) The results, which were comparable in premature and full-term infants, are grouped together in table II

Vaccination was usually successful the second time in infants that had not been infected and had not had an antibody response after the first vaccination (group 1) All the infants (10 out of 10) that had been infected initially but had not had a detectable antibody response became reinfected after the second administration of the same virus, and 8 out of 9 of them did have an antibody response (group 2) Reinfection was detectable in only 3 out of 9 infants in whom antibodies had developed after the original intestinal infection, but in 5 or 7 an increase in antibody titre was observed (group 3)

TABLE II—SECOND EXPOSURE OF INFANTS TO ATTENUATED VIRUS *

Group	Results of first vaccination	Results of second vaccination	
		Intestinal infection (no †)	Positive antibody response (no ‡)
1	Not infected, no antibody response	9 12	8 11
2	Infected, no antibody response	10 10	8 9
3	Infected, positive antibody response	3 9	5 7

* Summary of results in premature and full-term infants

† Numerator, those infected, denominator, those infected plus those not infected.

‡ Numerator, those with positive antibody response, denominator, those with plus those without response.

COMMENT AND SUMMARY

The results of this study indicated that infants 5–60 days old were more resistant to intestinal infection with poliovirus than the other age-groups investigated, but they usually had an immunological response, as shown by the presence of antibodies, when they did become infected In contrast, premature and full-term infants less than 5 days old were as highly susceptible to intestinal infection as infants more than 60 days old Nevertheless, despite a prolonged period of intestinal infection, premature and full-term infants less than 5 days old frequently failed to have a detectable antibody response. Infants older than 60 days almost invariably had an antibody response to intestinal infection with attenuated poliovirus

That newborn mammals are defective in their ability to produce antibodies in response to external stimuli has been reported by several workers[18] Hence it was not surprising to find the same defect in infants who were exposed in early life to living poliovirus In this study newborn premature and full-term infants did not differ

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18 Immunity and Resistance to Infection in Early Infancy Report of the 29th Ross Pediatric Research Conference, Columbus Ohio, 1959

in this respect Evidently the capacity to form antibodies is related to age rather than to maturity

It is more difficult to explain the relative resistance of the intestinal tract in infants 5–60 days old, which is preceded and followed by a period of higher susceptibility to infection with poliovirus Other investigations, which are summarised elsewhere, seem to indicate that this phenomenon is not related to the presence of congenitally acquired antibodies[9]

Presumptive evidence of tolerance to viral infection has been presented in the case of infection of turkeys with Rous sarcoma,[19] and in infection of mice with lymphocytic choriomeningitis virus[20] No evidence of tolerance to viral infections in man has ever been described The present results indicate that infants who failed to show an antibody response after an initial infection with poliovirus in early life are still capable of reacting immunologically on a second exposure to the virus Tolerance to infection with poliovirus has not been demonstrated in this study

It has been shown, however, that infants less than 60 days old are relatively resistant to intestinal infection with the attenuated virus, and that their immunological response is frequently inadequate Therefore administration of living attenuated polioviruses to these infants will probably not be as efficacious as vaccination with the same agents of infants more than 60 days old and cannot be recommended as a routine procedure

Two of us (J S P and S A P) are U S Public Health Service officers assigned to the Wistar Institute by the Communicable Disease Center, Epidemiology Branch, U S Public Health Service, our participation in these studies in no way implies endorsement by the Public Health Service These studies were supported by a grant from the U S Public Health Service, National Institute of Allergy and Infectious Disease

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Medical Societies

MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES

Systemic Treatment of Trichomonas Infestation

A MEETING on May 27, with Dr E E PREBBLE (Liverpool), the president, in the chair, was devoted to the use of 'Flagyl' (8823 R P, May & Baker), a derivative of nitroimidazole, in the systemic treatment of *Trichomonas vaginalis* infestations

Mr A J KING (London Hospital) referred to the first reports of the use of flagyl[1] and their confirmation[2,3] A therapeutic trial had been carried out conjointly at the venereal-disease clinics of the London Hospital (by Dr Philip Rodin), and of St Thomas's and St Bartholomew's (by Dr C S Nicol) At The London a total of 82 women entered the trial Knowledge of the natural persistence and transmissibility of the parasite, and of the inefficacy of the earlier oral remedies, made employment of untreated controls unnecessary

The dosage of flagyl was 200 mg three times daily by mouth for seven days No local treatment was given In the follow-up, routine culture of the vaginal secretion for *T vaginalis* and candida were carried out twice weekly for the first two weeks, weekly for the next four weeks, and then twice more after subsequent menstrual periods

Of the 82 patients treated, 78 (95%) were classed as immediate successes 52 continued under detailed observation, 3 were among the 4 immediate failures, and 6 others later relapsed or were reinfected, giving a success-rate of 83% over the full three months In 2 of the early failures there was evidence that not enough tablets had been taken In the other 2, serum levels of the drug were the two lowest of the nine estimated In the 6 later failures there was presumptive evidence of reinfection In the majority of patients the symptoms and signs resolved, with a decrease of leucocytes in the vaginal secretion and a fall in the pH by one to two weeks after treatment *T vaginalis* had disappeared from the secretions of 34 of 36 patients examined half way through the course of treatment Cultural studies yielded no evidence that flagyl either favoured or inhibited the growth of candida species

20 male patients with *T vaginalis* urethral infestation were treated with the same dosage In no case was the organism found after treatment, but signs of urethritis persisted in 2 patients with stricture, in 1 with littritis, and in 1 with prostatitis

One patient developed a shortlived scarlatiniform rash the day after treatment ended Minor gastrointestinal and oral side-effects were noted in 13 Transient leucopenia at the completion of treatment was detected in 3 of 41 patients

Dr C S NICOL described the results obtained by using 200 mg three times daily for five days In the 122 patients available for follow-up there was an immediate success-rate of 96% failure occurring in 5 cases As the period of follow-up lengthened, the parasites reappeared in a further 12 cases, giving an overall failure-rate of 14% 12 of the 17 patients who failed to respond admitted further sexual exposure A consistently low serum concentration of the drug was demonstrated in 1 case during re-treatment with an increased dose Among 11 males treated for five days there were no immediate or late failures The only toxic effect noticed was a complaint of vomiting by 1 patient Dr Nicol pointed out that he was giving an interim report, and it appeared inadvisable at present to put a five-day course into general use

Dr PIERRE DUREL (Paris) said that in prostitutes higher failure-rates had been found—6 out of 23 (26%) with oral treatment, and 13 out of 40 (33%) with flagyl pessaries In urinary excretion studies he had noted slight accumulation of the drug at doses above 500 mg daily He had also demonstrated that flagyl had no effect on fecundation in pregnant female rats

Dr G W CSONKA (Central Middlesex Hospital) in a double-blind trial had had only 2 failures in 46 patients treated with 200 mg three times daily for ten days The parasite persisted in 93% of the untreated group

Dr M SCOTT GRAY (Edinburgh Royal Infirmary), treating 67 females in three groups receiving courses of five, seven, and ten days, had obtained immediate cures in 94%, 96%, and 86% respectively Relapse was commonest at the end of the prescribed period of sexual abstinence She had found that serum levels of the drug in a newborn infant approximated to those in the mother whose treatment had continued into labour

Dr J CHESNEY (Endell Street Clinic) reported 4 failures in 41 women followed up for two months

Dr ELISABETH REES (Liverpool Royal Infirmary) reported an early clinical and bacteriological improvement in the majority of 38 women given 200 mg three times daily for seven days 1 patient developed a papulo-squamous eruption on the arms

Dr R R WILLCOX (St Mary's Hospital) had had immediate failure in 6% of 40 cases and late failure in 17% The commonest time for relapse was between the twenty-first and twenty-ninth days after treatment

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1 Durel P Roiron, V, Siboulet, A, Borel, L J *C R Soc franç Gyn* 1959, 29 36

2 Sylvestre L Gallai Z, Ethier, S Premier Symposium Canadien sur les U V G Montreal 1959

3 Durel P, Roiron V, Siboulet, A, Borel, L J *Brit J ven Dis* 1960, 36 21

Dr R. D CATTERALL (Leeds), finding flagyl effective in 12 cases out of 14, had treated 13 more females and 8 males with success in all and no evidence of leucopenia

Dr A C C DAVEY (Manchester Royal Infirmary) had succeeded in 43 of 46 patients 2 of the 3 failures were probably due to reinfection

Mr KING, summing up, spoke of the need for further studies of absorption in cases of early failure and suggested that the poor response to flagyl pessaries might be due to continued urethral infestation Because of the difficulty in detecting the parasites in males there seemed to be a case for treating male consorts in whom the parasite was not found.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE

Schistosome Infections as Zoonoses in Africa

A MEETING was held in London on May 19, with Sir WILLIAM MACARTHUR, the president, in the chair

Dr G S NELSON said that until recently it was believed that the transmission of *Schistosoma mansoni* and *S hæmatobium* in Africa was entirely inter-human and that "bovine" schistosomes rarely infected man. Recent work in Kenya, however, indicates that baboons may be important hosts of *S mansoni*, and it is now also known that man is frequently infected with "bovine" schistosomes Of the ten species or varieties of schistosomes reported from man in Africa, some are suspected of being hybrids between human and animal schistosomes Experimental infections with human schistosomes have been successfully carried out in many animals, but the best laboratory hosts are seldom found infected in Nature, and likewise the predominantly animal schistosomes have comparatively seldom been found in man

Infections with *S mansoni* were reported in *Cercopithecus sabæus* monkeys on the island of St. Kitts in the West Indies in 1928, but the present study stemmed from investigations of atheroma in baboons in Kenya made by an American research team led by Dr N Werthessen The team comprised a parasitologist and pathologists who carried out very detailed necropsies on 150 baboons Ova resembling those of *S mansoni* were found incidentally in the fæces of 4, and a detailed search of the liver and intestines resulted in similar ova being found in 24% of the series Dr Nelson then recovered adult schistosomes from 10 out of 12 baboons from the same area as that in which the initial series was obtained Both adult parasites and ova were identical with *S mansoni* from man, and the pathological changes in the baboons resembled those in humans This exciting finding prompted an investigation which is still proceeding into the importance of non-human primates in the maintenance of schistosomes in East Africa. To date 144 primates have been examined, and *S mansoni* has been found in 35 of 64 baboons from endemic areas but in none of 19 cercopithecus monkeys from the same areas In a *S hæmatobium* endemic area 1 out of 8 baboons was found to be infected but only 1 out of 25 cercopithecus monkeys No infection has been found in 25 baboons or monkeys collected from uninhabited national parks The evidence therefore suggests that the baboons have contracted their infections from man, but that they are good hosts of *S mansoni* Their gregarious nature, together with their fondness for living close to snail-infested water, may facilitate transmission among themselves, and they must be regarded as a potential source of increased *S mansoni* transmission to man.

Dr P E C. MANSON-BAHR emphasised that the lesions found in the baboons closely resemble those in human beings infected with *S mansoni* It was thought that schistosomiasis among baboons is a comparatively recent development and that they have probably been infected from man Dr Manson-Bahr also emphasised that the isolation from animals of a parasite similar to that found in man does not mean that the parasite is the same as the human variety Thus many leishmania appear identical but are probably different species

Dr C A WRIGHT drew attention to the changing nature of species All species should be regarded as being in a process of development there are probably dozens of different strains of schistosomes adapted to different conditions in different areas, and those found in the baboons are but one sub-variety

New Inventions

METHOD OF APPLYING A FULL-LENGTH LEG PLASTER FOR FRACTURES OF TIBIA AND FIBULA

IN the usual method of applying a full-length leg plaster for closed fractures of the tibia and fibula, the leg hangs over the table end from knee level After any necessary manipulation a short leg plaster is applied while the limb is held up This is difficult the plastered limb is heavy, the correct rotation of the foot relative to the knee has to be maintained, and the short plaster must be held in correct alignment with its extension over the knee and thigh, for otherwise the upper edge of the short plaster will press into the leg on one or other aspect. Furthermore, the manœuvre of extending the knee while the plaster is still short involves the risk of displacing the fracture.

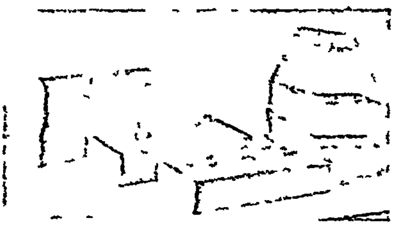

Fig 1

To overcome these difficulties a method has been devised in which, by the use of a series of blocks of variable height (fig 1), the fracture can be reduced and the reduction stabilised while a full-length plaster is applied

The patient and the blocks must be supported on a firm level surface, I use a rectangular wooden board designed to rest on an operating-table or trolley (fig 2) Knee flexion of a desired amount can be achieved by varying the position and height of the blocks Traction and manipulation can be performed with only the proximal block in position, then the distal block is

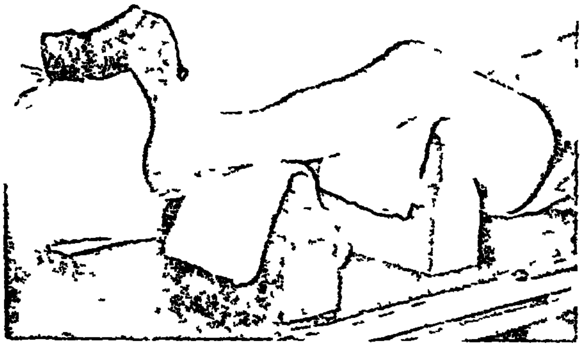

Fig. 2

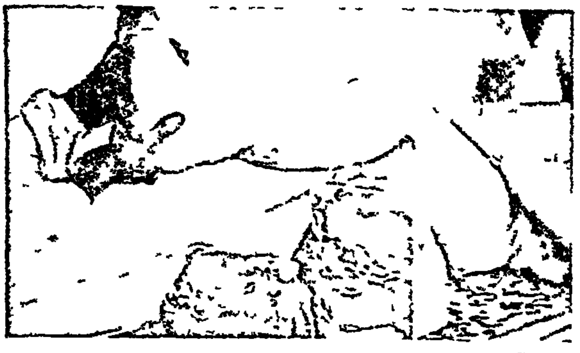

Fig 3.

adjusted in height and position to support the fracture alignment—three blocks may be used in certain cases Each block is covered by a wool strip before it is put in place, and the wool strip is incorporated in the lining of the plaster It is best for the operator to control the position of the foot while a competent assistant applies the full-length plaster When the plaster has set, the blocks can be removed and the gaps which are lined by wool (fig 3) are covered

This method is of particular value when there is a shortage of assistance It is equally applicable to closed and to open fractures

St George s Hospital,
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DAVID F THOMAS
F R C S

Reviews of Books

A Practice of Anæsthesia

W D WYLIE, M.B , M R C P , F F A R C S , consultant anæsthetist, St Thomas's Hospital, The National Hospital for Nervous Diseases, and The Royal Masonic Hospital, London, H C CHURCHILL-DAVIDSON, M D , F F.A R C S , consultant anæsthetist, St Thomas's Hospital, The Chelsea Hospital for Women, and The Brompton Hospital, London London Lloyd-Luke (Medical Books) 1959 Pp 1056 105*s*

THIS first comprehensive textbook of anæsthesia by an English author to appear for some years is a worthy representative of British practice

It differs from the usual plan in that it is divided into sections dealing with the respiratory, cardiovascular, nervous, digestive and excretory, endocrine, and reproductive systems This leads to such surprises as a consideration of neostigmine-resistant curarisation under " lung function ", and to some repetition Dr Wylie and Dr Churchill-Davidson have written most of the book, but seven others have also contributed One of the best of these contributions is the section on pain and its treatment by Dr J D Laycock In the section on the mechanism of narcosis, by Dr C A Foster, there is surprisingly no mention of Ferguson or Mullins The book has very few omissions of importance, however, and the student will find it helpful on nearly every aspect of anæsthesia The sections on cardiovascular physiology and on neuromuscular block are very good, reflecting the authors' wide experience They are less at home in the physics of anæsthesia, and not everyone will agree with such phrases as " negative suction pressure " in discussing cabinet respirators

There are two or three pages of useful biochemical and physiological values and conversion factors (the title " vade mecum " is inapt for this integral part of a book weighing 5 lb) The formula for the conversion of Centigrade to Fahrenheit is wrong The book is well produced and adequately indexed, and the many illustrations are nearly all apt and clear

Pediatric Neurosurgery

Editors IRA J JACKSON, M D , M SC , F A C S , RAYMOND K THOMSON, M D , F A C.S Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1960 Pp 564 125*s*

THIS book has been written by 24 contributors from all parts of the United States and all types of practice The first seven chapters on general aspects have been written mainly by non-surgical specialists and deal with diagnosis, the general management of surgical patients, anæsthesia, associated plastic surgical problems, and diseases which may be confusing in diagnosis but which do not usually require surgical treatment The second part is concerned with specific neurosurgical problems At times one senses perhaps that some of the contributors are possibly more at home with the adult than the small child The section on head injury is clear and good but the recommendations about the use of hypertonic solutions are perhaps too generous for children, and sponging with tepid water rather than ice-cold alcohol is possibly more effective in controlling hyperthermia It is striking to notice in several sections how readily American surgeons resort to tracheostomy, and this emphasis may help to encourage the wider use of this valuable procedure The contrasts in the type and situation of brain tumours in children and adults are well shown in an excellent chapter on cranial and intracranial tumours

This book can be recommended for reference purposes to all surgeons who have to treat children with neurological diseases and for more general use to neurosurgeons

Health and Happiness in Old Age

CELIA WESTROPP, D M , M R C P , MOYRA WILLIAMS, D PHIL., B LITT London Methuen 1960 Pp 133 8*s* 6*d*

THIS admirable book, written by two of the staff of the Oxford Geriatric Unit, is largely based on experience gained by the Nuffield Mental Health Research Team in Oxford during the past five years The book is designed to help nurses, social workers, and the families of old people It is not written primarily for doctors but it can hardly fail to be of use to them In a simple, scientific, but not aggressively " popular " manner it discusses the physical and mental changes in old age and gives many helpful suggestions about their management The psychological parts of the book are outstandingly good and are more intelligible than many textbooks of psychiatry or medicine

It is hard to imagine a better book for anyone whose professional or domestic responsibilities include the care of old people, and who seek to understand them better Those who are beginning to contemplate their own old age will also find much here to help them

High Blood Pressure and Pregnancy

LANCE TOWNSEND, M D , F R.C S E , F R C O G , *professor of* obstetrics and gynæcology, University of Melbourne Melbourne Melbourne University Press London Cambridge University Press 1950 Pp 530 40*s*

THIS little monograph attempts to evaluate the effect of maternal hypertension in pregnancy in both mother and child. Progress in management is studied by comparing results in a series of cases treated in 1946 with those in another series ten years later, when a number of modifications in treatment were in force Unfortunately, as the author points out, the series are too small to allow each modification to be evaluated separately, and so the main conclusions are about the overall picture Nevertheless, he clearly shows that the results in the 1956 series are better than in the 1946 one, though just *how this has* been achieved is by no means clear, because so many factors are involved

The book is of interest mainly to workers in this particular and very specialised branch of obstetrics, and though the critical reader may quarrel with some of the deductions, the data so clearly presented are valuable and worthy of publication

A Symposium on Immunisation in Childhood (Edinburgh E & S Livingstone 1960 Pp 139 17*s* 6*d*)—At this important international gathering, held in the Wellcome Building, London, on May 4–6, 1959, some 70 experts surveyed the field of immunisation as it concerns us in the West Despite conflicting evidence the safety of diphtheria-pertussis-tetanus triple prophylactic was endorsed, and the L C C 's thorough organisation had not recorded any provocation poliomyelitis from over $^1/_4$ million injections Vaccination against smallpox seems to cause least trouble between the ages of 1 and 4 years, and poliomyelitis immunisation is apparently safe For mass administration of vaccine, now undoubtedly requiring a syringe and needle per patient and very careful sterilisation, a disposable 6*d* unit has many attractions Some uniform system of records both for general practitioners and for patients (especially for tetanus) is urgently needed (the symposium did not reflect on the possibility of electronic methods in abstracting emergency information from a number of regional centres) Two schedules of immunisation were prepared with 7 and 10 injections respectively during the first eighteen months Practical experience here and in other countries led most people to favour the shorter schedule The material of the symposium has been admirably digested to its essentials though it remains easy (and very useful) reading

THE LANCET

LONDON 4 JUNE 1960

Other People's Mistakes

We all make mistakes and some of us make more mistakes than others What is new about this platitude is that we make more mistakes today than were made fifty years ago, and what may happen fifty years hence is alarming to contemplate The bulk of useful information available to us all is increasing by leaps and bounds, but a steadily diminishing fraction of it can be mastered by individuals Any up-to-date physician must be horrified to discover in surgical wards medical ailments still treated according to the canons of his student days, the surgical tyro could turn a visit to ostensibly medical patients into a field-day, and only weariness prevents the pathologist from being appalled by the clinical habits of both

The management of acute abdominal emergencies reflects this trend Such emergencies are common enough to be dealt with by doctors of widely differing experience in a variety of circumstances, they demand prompt decisions, and potentially all are fatal We have come to recognise, moreover, during the past twenty years that occasionally the ætiology of an "acute abdomen" lies in the province of specialists whom surgeons a generation ago regarded as amiable cranks We need not linger over tabetic crises, which few young doctors have ever witnessed but which to many still epitomise the "medical causes" of acute abdominal symptoms Like lead-poisoning, incipient diabetic coma, or herpes in the prevesicular stage, it is still likely to be missed, but it is unlikely to be missed out of sheer ignorance Hæmatological crises, metabolic abnormalities, and iatrogenic illnesses, on the other hand, may end in disaster or near-disaster for no other reason

Every now and then bleeding diseases present with digestive symptoms, abdominal tenderness, guarding and even rigidity, moderate fever, and leucocytosis If the patient were not a hæmophiliac, the differential diagnosis would revolve around acute appendicitis with peritonitis, and the emergency surgeon might properly be guided by the best-tried of all surgical catch-phrases, and look and see rather than wait and see In fact the patient has probably sustained a retroperitoneal hæmorrhage, he is probably bleeding still, and, even should he have peritonitis, this calls for the utmost effort with conservative treatment Casual acquaintance with current literature, unfortunately, misleads Medical journals from time to time publish accounts of long and arduous operations successfully carried out in specialised centres on "bleeders" But failures are less readily reported, and nobody keeps count of the much larger numbers who die Thus even the surgeon who elicits a history of abnormal bleeding, or (less commonly) makes a tentative diagnosis on physical signs, often proceeds with the vague but comforting notion at the back of his mind that such emergencies can be dealt with nowadays by a choice of potent laboratory concoctions more or less as they arise Later, when the panic has died down (the patient having died), he will learn that nine out of ten laboratories are still unequipped to deal with such cases, and he may feel indignant that this information was not conveyed to him before the operation

Over the past few years acute porphyria has gradually percolated into surgical consciousness, but hæmolytic crises have not They can present with all the trappings of a major intraperitoneal catastrophe—nausea, vomiting, headache, rigors, tenderness, guarding, rigidity, leucocytosis—and they can strike from the blue, with no hæmatological past history The causes of acute hæmolysis are legion (and increasing as new drugs increase), and rarely do they conform to the small-print paragraphs which many surgical texts, now in their umpteenth edition, include as pious memorials to the first The hæmoglobinopathies have especially come to the fore not in all of them do the red blood-cells sickle, and in many the anæmia remains slight In these patients the dark skin commonly masks the jaundice (if present); language difficulty can mar the history, and mental symptoms (which not uncommonly coincide with the abdominal crisis) can add to the confusion But even if an otherwise unexplained anæmia attracts attention, many an emergency surgeon will order six pints of blood "to be on the safe side" rather than seek expert advice—if such advice is, in fact, obtainable The diagnosis, unfortunately, cannot be made at routine postmortem examination, and another death on the table will remain unexplained

Collagen diseases, too, may present as acute abdominal emergencies Severe abdominal pain, fulminating gastro-intestinal ulceration, intraperitoneal and retroperitoneal hæmorrhage, or mesenteric vascular thrombosis can be the dramatic first manifestations of polyarteritis nodosa. and now and again a patient with disseminated lupus erythematosus comes to hospital as a case of acute peritonitis or acute pancreatitis (A similar picture is occasionally seen in an acute crisis of hæmochromatosis) Operation may, of course, be necessary in such cases, but only an inkling of the ætiology will turn it into a rational procedure The emergency admission of previously diagnosed and treated patients is potentially at least as dangerous Despite oft-repeated warnings, cortisone and similar hormone preparations are still prescribed with too little thought of future surgery For no obvious reason children can die under anæsthesia months or even years after discontinuation of such therapy, unless the danger is realised and precautions are taken

Specialisation in medicine has long passed the point of no return, and for any one of us to keep up with all the specialist Joneses is neither possible nor desirable But we could still try to adapt our methods to the situation we have created A medical traveller from space would marvel at the galaxy of surgical talent that circled aro the senior surgeon, and he would compliment the fessor of medicine on the aura of medical wisdom that emanated from his even more numerous retinue But lack of medical thought among the former and dearth of surgical acumen in the latter would lead him to believe that the human frame was heir to no more than one disease at a time, and that diseases conveniently grouped themselves into current specialties Only when disabused would he begin to wonder how many medical emergencies would have to be operated on unnecessarily and for how long surgical cases would have to languish on drugs and diets before one of the surgical registrars could be spared for the medical firm, a medical registrar for the surgical firm, and a clinical pathologist for both

Giants with Cold Feet

EVEN in the twentieth century there are many thinly populated and almost unexplored regions in the world, and in several of these there have arisen rumours of the existence of large animals still awaiting scientific discovery and classification The publicity accorded to the "abominable snowman" of the Himalayas is no doubt a tribute to the aura of mystery and endeavour surrounding the highest mountain on earth It may also be due in part to the beguiling name bestowed upon the creature, almost certainly as a result of a losing battle with the local dialect As ASHER [1] has put it "There is something about a name, particularly an eponymous term, which brings into being things which never seemed to be there before"

What little is known about the "snowman" has been documented by HEUVELMANS [2] Sightings by the local population appear to have been fairly frequent, but few foreigners have been so fortunate, the odds against a direct encounter are naturally high in an area where search parties stand out distinctly against the snow Various portions of snowmen are said to be preserved in the local monasteries, and a supposed scalp has been subjected to investigation without any very conclusive results Witnesses usually describe the animal as an erect or semi-erect biped rather smaller than a man, and many tracks discovered in the snow by competent observers tend to confirm this estimate of size. But one of the best photographs of a footprint from such a track—that taken by SHIPTON in 1951—is a massive affair approximately $12^1/_2$ in long, $7^1/_2$ in broad at the forefoot, and $6^1/_2$ in broad at the heel The great toe is thick and stumpy, and seems to take much of the weight, the second is the longest toe, and is separate from the hallux and third toe, the lateral three toes are small and partly fused If the footprints of SHIPTON's animal are in proportion to its general build we are dealing with something much larger than a small man and more comparable to a giant Possibly there are two species, or, more simply, a considerable difference in size between the sexes

At first those unwilling to entertain the suggestion of an unknown animal put forward the view that the prints were made by a langur—a long-tailed monkey standing about 4 ft 6 in to 5 ft high and known to exist in the area The fact that the langur's foot is of wholly different construction and size from the foot postulated from SHIPTON's prints was countered by suggesting that the snow round each print had melted and then refrozen There is no supporting evidence for such an idea, which takes no account of the sharpness of the outline, the length of the stride, the absence of any marks from the tail, and several other factors More plausible was the suggestion that the prints were those of a bear, but all the information from the many tracks so far discovered seems to point to a bipedal mode of progression, and these "bears" would have had to walk on their hind legs for many miles to produce anything resembling the recorded evidence In any case, the local inhabitants have no hesitation in differentiating between the tracks of snowmen and of bears

If we do not accept the bear or the langur, what have we left? HEUVELMANS suggests that we have a very large plantigrade bipedal primate, possibly of similar type to the fossil *Gigantopithecus*, whose teeth were discovered in China in 1934 He has in fact gone so far as to give it the provisional name of *Dinanthropoides nivalis* Recently TSCHERNEZKY,[3] using SHIPTON's original photograph, has made a model of the snowman's foot and compared it with those of a gorilla, a langur, and a bear His conclusions are identical with those of HEUVELMANS, except that he thinks that the hallux is opposable TSCHERNEZKY suggests that the hallux has a much shortened metatarsal element,[4] the phalanges being large Such a toe, he believes, would be capable of grasping, but less effective for walking upright, so that the second toe has become elongated and thickened in compensation He considers that the print indicates that the animal walks in a manner similar to man A medially disposed functional axis of the foot[5] would accord with the suggestion that the animal is an anthropoid If such a creature exists, its home may be below the snowline, its excursions up the mountain sides being dictated by a need for salt, which is contained in lichens growing on the rocks Droppings discovered in relation to the tracks indicate an omnivorous diet, including vegetation which is not present at high altitudes It has also been suggested that the creature may not be habitually bipedal, but adopts this gait to make as little contact as possible with the cold snow Nevertheless, this animal is sufficiently adept on two feet to travel for long distances over difficult terrain without apparently putting its forelimbs to the ground

In the absence of fuller evidence it is clearly unsafe to speculate on the detailed structure and appearance of the snowman, but the arguments set out by HEUVELMANS and TSCHERNEZKY must be taken seriously Now that the Himalayas are more frequented by mountaineers than formerly, information is likely to accumulate more rapidly, and this most popular of mysteries may become a mystery no more

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[1] Asher R *Lancet* 1959 ii 359

[2] Heuvelmans B On the Track of Unknown Animals London, 1959

[3] Tschernezky, W *Nature, Lond* 1960, 186 196

[4] Wood Jones, F Structure and Function as Seen in the Foot London 1949

[5] Le Gros Clark, W F The Antecedents of Man Edinburgh, 1959

Annotations

VOLUNTARY ISOLATION

WHEN men go to the inaccessible polar regions their exile, though voluntary, is irrevocable. What are the psychological stresses upon them? There is little strictly medical information available, although, over the years, excellent reports have been written—for example, by Priestley[1] and Byrd,[2] and by Scott,[3] whose restrained writing had a specially dramatic impact. Lately Dr Philip Law, a geographer and director of the Antarctic division of the Australian Department of External Affairs, has discussed[4] the personality problems of men serving in the Antarctic. He has the unique experience of 30 expeditions over the past twelve years.

Once the men settle in their isolated camp, problems of personality are more serious than those of weather. Avenues of escape are restricted, and there is little chance of hiding weaknesses: even the desire to hide them disappears. People are shown in their true colours—in fact, there is little point in keeping up pretences. If tensions develop, they may be between individuals, between groups, or between the men and the leader. But when disaster threatens, differences are forgotten, and the history of polar exploration contains descriptions of the noblest acts of unselfishness.

What is the basis of social grouping in expedition parties? The expeditions of Scott and Shackleton were by no means classless. They were based on strict Naval upper deck and lower deck discipline. Recent ventures like the British North Greenland Expedition (1952–54) and the Commonwealth Trans-Antarctic Expedition (1955–58) were completely democratic, as is the Falkland Islands Dependencies Survey. They are classless societies at the outset, but soon a grouping seems to develop and in the case of the Australian National Antarctic Research Expeditions it had much to do with the men's education.

Intelligence seems to be the most important non-physical aid to survival. Law suggests that "the man of low basic intelligence will crack up before his frailer intellectual companion", but this does not strictly accord with general experience, since the intellectual (as opposed to the intelligent) may also have an over-vivid imagination, which is a disadvantage in the polar wastes. The ignorant phlegmatic man may not suffer if he has simple faith in his instructions. A certain type of newly graduated scientist, unworldly but intellectually arrogant, seems a positive menace; he has a burning sense of "freedom of the individual" which runs to lack of discipline in his work, late rising, and neglect of personal hygiene.

The question is not only how to select the best men but also how to avoid the difficult ones. Lewis and Masterton[5] feel that there is no such person as an "expedition type". There are certain valuable characteristics, such as a good sense of humour, ability to get on with other people, and honesty, and Law adds unselfishness and tolerance. The overriding criterion is that a man should be efficient at his job, especially since work is the most meaningful of the social roles of isolated men. If a man is good at his job he will overcome personality deficiencies and even gain special respect. "Joe is a regular stinker as a bloke but he's a damn good diesel man."

More attention might be paid to some subtleties that would go unnoticed unless specially looked for. A man who tends to be mildly querulous at home might, in the stress of a crowded winter hut, seem to his fellows almost paranoid; a tendency to over-confidence might be downright dangerous. Any personal animosities existing at home between two prospective members should disqualify one of them. For the smaller expeditions, selectors in Britain look for the highest motives, and are likely to refuse a man who wishes to be a refugee from civilisation. Law's view is more generous, and he feels there is a place for such a man who can be sublimely happy in his isolation.

It has been shown[6] that in spite of the irregularity of sleep on a polar expedition the total amount of sleep taken is approximately 8 hours in 24. The study of sleep and wakefulness is particularly interesting because a polar expedition is one of the rare occasions when men are not completely governed by the usual timetables of organised society. Sleep-wakefulness data from expeditions may indicate more closely the biological demand for sleep.

Polar expeditions may be looked on as human laboratories[7] and if the effect of cold itself can be identified there is no reason why they might not serve a much wider scope of human investigation, including psychological studies. The personality problems should be put into the correct perspective, however, since most men can work, and be fit, comfortable, and happy for long periods under unusual climatic and social conditions which might seem intolerable from a distance. If neurotic behaviour does arise it seems to clear up when the man leaves the polar regions.

ASYMPTOMATIC BACTERIURIA

MOST urologists recognise that some degree of urinary infection, short of overt sepsis, is commonly associated with genitourinary surgery and indwelling catheterisation, but the consequences seldom seem to be serious—perhaps largely owing to free drainage and routine prophylactic chemotherapy. On the other hand, the belief that permanent renal damage can follow asymptomatic bacteriuria as the result of simple instrumentation is supported by clear instances in which severe infective complications such as acute pyelonephritis and even septicæmia have ensued, and more chronic, and possibly hidden, infections may lead to progressive deterioration of renal function and ultimate failure.

At the Beth Israel Hospital, Boston, Kaitz and Williams[8] found 53 cases (17%) of significant bacteriuria among 309 general admissions in a ten-week period. Their study was based on examination of "clean voided specimens" which were refrigerated after collection and cultured within forty-eight hours. A bacterial count of over 100,000 viable organisms per ml was regarded as a significant bacteriuria. Only patients over 50 years of age were considered, and Kaitz and Williams state that of those with bacteriuria all the men and half the women had previously undergone urinary-tract instrumentation.

Of those without bacteriuria on admission the urinary-tract infection developed in each case after catheterisation (infection developed in 13 out of 41 catheterised patients)

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[2] Byrd, R Alone London, 1938
[3] Scott, R F Scott's Last Expedition London, 1913
[4] Law, P Med J Aust 1960, i 273
[5] Lewis, H E, Masterton, J P Lancet, 1955, ii, 494, 549
[6] Lewis, H E., Masterton J P Ibid 1957, i, 1262
[7] Goldsmith R Lewis H E J occup Med 1960 2 118
[8] Kaitz, A L., Williams, E J New Engl J Med 1960 262, 425

Of the group admitted with bacteriuria an equal number of clinical infections became manifest before and after catheterisation

It is extremely difficult to determine the significance of these findings in relation to permanent renal infection, for no clear evidence is given on this point The important feature of this study is not so much that bacterial urinary infections in the elderly sick are much commoner than their symptoms suggest (an already well-established fact) but that the number of overt infections following catheterisation can be disturbingly high unless strenuous precautions are applied by means of asepsis and chemotherapy

MAGNESIUM-DEFICIENT TETANY IN MAN

TETANY and convulsions due to experimental magnesium deficiency were shown in 1932 to occur in rats,[1] and later in dogs, guineapigs, and rabbits [2–4] Magnesium-deficient tetany is familiar to veterinary surgeons as a spontaneous disease in cattle—the so-called "grass staggers" Suggestive case-records of tetany due to magnesium deficiency in man have been published,[5–8] but Vallee et al [9] have now reported the best-documented and most convincing series so far described They describe five cases of tetany in which other causes were reasonably well excluded and which seemed to respond only to treatment with magnesium salts

The deficit of magnesium was in no case due to dietary deficiency alone Two of the patients lost magnesium excessively in vomit or intestinal secretions removed by continuous suction, two were receiving large volumes of magnesium-free fluids parenterally, and one had an intestinal absorption defect The tetany was indistinguishable clinically from the more familiar type due to calcium lack All the patients had either spontaneous carpopedal spasms or a positive Chvostek or Trousseau sign Three had generalised convulsions and four athetoid movements of the extremities The serum-magnesium level when the tetany was maximal ranged from 0 6 to 1 33 mEq per litre—considerably below the normal range of 1 75 to 2 5 mEq per litre The serum calcium, potassium, sodium, phosphate, chloride, bicarbonate, and protein values were either normal or only slightly abnormal In all patients the tetany was immediately relieved by intramuscular injections of 2–4 ml 50% magnesium sulphate solution given four-hourly In one patient the tetany recurred after the injections were discontinued, but promptly responded to further injections of magnesium sulphate

While this is the most persuasive report of magnesium deficiency tetany so far published, there are gaps which may prevent the sceptical reader from regarding magnesium-deficient tetany in man as a completely proved clinical syndrome The serum-calcium values of the patients are reported as ranging from 4 40 to 4 75 mEq per litre—values which in most laboratories would be regarded as undoubtedly below the lower limit of normal Vallee et al say that the normal range of serum-calcium is 4 5 to 5 5 mEq per litre, but most laboratories give a narrower range of 4 75 to 5 25 mEq per litre The evidence afforded by the response to magnesium therapy would have been strengthened if the cases had previously been shown to be unresponsive to injections of calcium gluconate Moreover, the reverse control of studying the effect of magnesium injections in cases of mild hypocalcæmic tetany is not reported This note of caution is the more necessary since tetany is always produced by a summation of the varied effects of many cations on muscle and nerve, calcium being usually regarded as the most important single example We hope that further investigations will soon remove all doubt that this valuable paper describes a proven clinical syndrome in man

Vallee et al suggest that lack of magnesium in man is likeliest with a combination of decreased intake and excessive loss of this element This combination is especially liable to be found after protracted parenteral administration of magnesium-free fluids to patients with severe vomiting and diarrhœa or with intestinal suction drainage Excess loss of magnesium in the urine is less likely since in the presence of an established magnesium deficit the normal kidney effectively retains magnesium in the body [10] One of Vallee's patients was a chronic alcoholic in whom delirium tremens developed after therapy had relieved the tetany This disproves an earlier view [11 12] that magnesium deficiency may be the cause of the neuromuscular irritability of delirium tremens

Other symptoms and signs referable to magnesium deficiency, according to Flink et al ,[13] include muscular twitching and tremors, profuse sweating, tachycardia, psychological abnormalities ranging from mild anxiety to severe agitation, delirium with hallucinations, confusion, disorientation, and rarely convulsions and coma Intensive investigation is rapidly elucidating the physiology and pathology of this hitherto rather neglected but important body cation [14 15]

CHOLINE SALICYLATE

THE quest for an effective salicylate, free from undesirable side-effects and pleasant to take, continues Choline salicylate, a new compound in therapeutics, was tested by Davis et al [16] in rheumatic fever and rheumatoid arthritis The antipyretic and anti-inflammatory effects were found to be comparable with those of aspirin in corresponding doses, and the analgesic effect in rheumatoid arthritis was also similar, as a rule, larger equivalent doses than aspirin were tolerated The side-effects were tinnitus and pyrosis

Broh-Kahn,[17] who has been particularly concerned with the development of choline salicylate, reports that it is extremely soluble in water, a saturated solution containing 96% of the substance by weight, being hygroscopic it can be kept only as an aqueous solution He finds that, administered orally, it is absorbed about four times as rapidly as aspirin, and peak plasma levels are reached in ten minutes—that is, twelve times as quickly as aspirin Broh-Kahn describes the findings of eighty investigators who gave the drug to 1200 patients and compared it favourably with aspirin. Its action was rapid, and the incidence of pyrosis, nausea, and vomiting was lower than with aspirin. Another possible advantage over aspirin is the ease of administration in liquid form to children and to those who have difficulty in swallowing tablets. The maximum tolerated dosage was higher than that of aspirin or sodium salicylate, but Broh-Kahn does not claim that it is preferable for all patients.

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[2] Orent, E R., Kruse, H D , McCollum, E V *Amer J Physiol* 1932, 101 454

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[5] Miller, J F *Amer J Dis Child* 1944, 67 117

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[8] Agna J W , Goldsmith R E *New Engl J Med* 1958 258 222

[9] Vallee, B L., Wacker, W E C , Ulmer, D D *ibid* 1960, 262 155

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[12] Flink, E B *J Amer med Ass* 1956, 160, 1406

[13] Flink, E B , McCollister R , Prasad, A S , Melby, J C , Doe, R P *Ann intern Med* 1957, 47 956

[14] Wacker, W E C., Vallee B L *New Engl J Med* 1958, 259 431, 475

[15] Barker E S *J chron Dis* 1960, 11, 278

[16] Davis, G M Moore P T , Siemsen, J K , Sode, J , Baber, W J *Amer J med Sci* 1960 239, 273

[17] Broh-Kahn, R H *Int Rec Med*, 1960 173, 217

Adequate therapeutic blood levels of choline salicylate were maintained easily by Wolf and Aboody[18]; significant blood levels were still present twelve hours after a day of therapy. Nevinney and Gowans[19] found that 40% of a group of arthritic patients preferred it to previously used salicylates. Thomas[20] regards choline salicylate as the drug of choice for arthritic conditions. Winter[21] has found it effective against headache and as an antipyretic.

While at this stage confidence would be rash, it does seem that choline salicylate will be a useful addition to everyday therapeutics.

AMYLOID DISEASE AND RENAL VEIN THROMBOSIS

MODERN therapeutic advances are arousing interest in conditions which, owing to their hopeless prognosis, were formerly regarded chiefly as pathological curiosities. One such condition is thrombosis of the renal vein in amyloidosis. Harrison et al.[22] showed that, in renal vein thrombosis, either the renal changes were secondary to venous obstruction or the thrombosis was itself secondary to primary renal disease, and in the latter group amyloidosis appeared to be an especially common cause. As past studies have not provided any convincing explanation for the association of thrombosis with amyloidosis, Barclay et al.[23] have studied nine cases with special reference to pathogenesis, clinical aspects, and therapeutic implications.

While in these cases the amyloid was secondary to some known predisposing cause, Barclay et al. point out that one example of renal vein thrombosis in primary amyloidosis has already been reported[24] and that Symmers[25] found the kidneys involved in 35% of cases of the primary type, so other reports of renal vein thrombosis in this type may be forthcoming. In fact, this association is probably much commoner than present reports indicate. From the distribution of the thrombi, Barclay et al. suggest that thrombosis occurs first in the glomerular capillaries largely under the influence of dehydration and the presence of increased fibrinogen, and thrombosis is propagated in the direction of the blood-stream along a few venules to the arcuate and interlobar veins, but only rarely reaches the main trunk. The original glomerular thrombi may be removed by the normal fibrinolytic activity, but the larger thrombi are not so susceptible and show various stages of organisation.

Harrison et al.[22] have described two varieties of clinical presentation of renal vein thrombosis—the sudden onset of a nephrotic syndrome, or rapid deterioration of renal function with oliguria and uræmia. Most of Barclay's[23] cases conformed to the latter variety, and he points out that in cases with amyloidosis (or any known renal disease) attempted confirmation of the diagnosis by venography may be dangerous as well as unhelpful. The importance of recognising the development of thrombosis lies in the possibility of anticoagulant therapy. One case diagnosed during life improved on such treatment for three months, but four months later the patient's general condition deteriorated and she died in cachexia. In another case diagnosed in life such treatment could not be given owing to a hæmorrhagic tendency. While amyloid itself may possibly regress spontaneously or some treatment may control it, renal vein thrombosis should be watched for and treated if it arises.

Barclay discusses the use of corticotrophin or cortisone in the treatment of the primary disease causing the amyloid: these hormones may increase or even cause amyloid, and further investigation of this point is urgently required.

CONFERENCE OF CONSULTANTS

THE second conference of consultants and specialists (the first was in 1956[1]) met in London on May 25 with Mr. A. M. A. Moore in the chair. Organised by the central and regional consultants and specialists committees, this conference aims to meet from time to time to discuss medicopolitical issues affecting the hospital service. It is not a policy-making body ("just a talking-shop" someone said bitterly), so its decisions are not binding on the Central Consultants and Specialists Committee. And that is how it will remain for the present, despite some unsuccessful efforts at last week's session to change its status and make the conference comparable to the annual representative meeting of the B.M.A.

The conference was deliberately timed for soon after the Royal Commission's report was expected, but in the event the Commission's findings did not occupy the conference for long or generate much contention. The meeting agreed readily enough with the Central Consultants and Specialists Committee's acceptance of the "package deal" offer of the Government, with the proviso that "there should be a clear understanding that acceptances of the report as it stands does not necessarily signify that we agree with the whole of the report or with all its recommendations". But little support could be summoned for a much stronger amendment which ended threateningly "we reserve the right to press our claims not already met". The general feeling seemed to be that enough pressing had been done for the moment and that the Commission's findings and their acceptance by the Government represented a substantial victory for the profession.

"This conference is dissatisfied with the present method of allotting distinction awards", proposed the South West Metropolitan region, and on this question feelings were almost evenly divided. The Central Committee had reaffirmed its support of the present system and expressed its confidence in Lord Moran and his committee, but it was clear that Mr. H. A. Kidd was voicing widely held misgivings when he criticised the high proportion of merit awards held by teaching-hospital consultants and the absence of representatives from non-teaching hospitals on the distinction-awards committee. In the end the conference recorded its dissatisfaction with the present system by 114 votes to 102.

Lord Moran and his committee had plenty of defenders in this debate, but the General Nursing Council had hardly a single supporter when the conference attack the Council's plans[2] for raising the standard required for the recognition of hospitals as nurse training schools The proposals are that a complete training school must have a minimum of 300 beds in one or more hospitals, with a casualty department, outpatient clinics, operating-theatres, and a number of other specified departments, and a daily average occupancy of at least 240 beds These changes were interpreted as too drastic they would remove recognition from many well-established and successful training schools and deprive some parts of the country of a training school, they would embarrass small non-teaching hospitals, they would lead to a serious shortage of nurses and the closure of hospital beds For these and other reasons, the meeting disapproved of what the G N C was doing, adding " the nursing curriculum should be mainly basic nursing, and special nurse training should be taken as a postgraduate" This indignation partly obscured the soundness of Dr C W Clayson's remark that no substantial advance in nursing recruitment could be expected until anomalies in the present salary structure had been eliminated

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[18] Wolf, J. W., Aboody, R. *ibid* p. 234.
[19] Nevinney, D., Gowans, J. D. C. *ibid* p. 242.
[20] Thomas, R. P. *ibid* p. 248.
[21] Winter, R. E. *ibid* p. 255.
[22] Harrison, C. V., Milne, M. D., Steiner, R. E. *Quart. J. Med.* 1956, 25, 285.
[23] Barclay, G. P. T., Cameron, H. MacD., Loughridge, L. W. *ibid* 1960, 29, 137.
[24] Chambers, R. A., Medd, W. E., Spencer, H. *ibid* 1958, 27, 207.
[25] Symmers, W. St. C. *J. clin. Path.* 1956, 9, 187.

[1] See *Lancet*, 1956, i, 1063.

TESTS FOR ANGINA PECTORIS

ANGINA pectoris is easily recognised if the history is typical, and an abnormal electrocardiogram (E C G) may strengthen the clinical diagnosis, but in many patients with chest pain the solution is not so simple, and Biorck[3] stated he could be certain of the diagnosis in only one out of every six cases of suspected angina Angina may be confirmed by detecting electrocardiographic evidence of coronary-artery insufficiency in certain circumstances —usually by exerting the patient or by making him breathe low concentrations of oxygen (earlier tests using adrenaline or pitressin have been abandoned as dangerous) To be of any use such a test must be positive in a high proportion of known cases of angina and negative in healthy subjects, but the reports on earlier exercise and anoxia tests were variable and disappointing Larsen,[4] using a mixture of 9% oxygen in nitrogen, obtained a positive result in slightly over 40% of 30 subjects with ischæmic heart-disease, and Levy et al,[5] using 10% oxygen, obtained positive results in 55%, Biorck[6] later obtained only 30% of positive results by Levy's method, but according to other reports about 50% are positive Master's[7] original reports of the two-step exercise test stated that 40% of patients with angina gave a positive response where the resting E C G was normal, but the proportion rose to 66% where this was abnormal Master[8] has since claimed a positive result in 95% with his present exercise test, but this has the serious drawback that 6% of control subjects also give a positive result Wood et al[9] have reported a positive response to exertion in 88% of patients with typical angina, and found a similar curve in only 1 out of 100 normal controls They attributed their high proportion of positive results largely to the fact that their patients were subjected to maximal effort rather than a standard amount as in earlier tests

With these discrepancies in mind, Coulshed[10] has reinvestigated Malmstrom's[11] modification of Levy's anoxia test in 111 patients of whom 53 were suspected of having ischæmic heart-disease, and 7 others with intermittent claudication without angina 41 patients without clinical cardiovascular disease acted as controls, while another 10 had various conditions without symptoms of ischæmic heart-disease The gas mixture used by Malmstrom consisted of 6 5% oxygen, 4 5% carbon dioxide, and 89% nitrogen, which produces a more rapid and consistent fall in arterial oxygen than Levy's original 10% oxygen in nitrogen, and eliminates both alkalosis and changes in arterial pH, thus preventing possible ST deviation due to these causes An identical mixture was used by Coulshed and administered through a standard anæsthetic machine for ten minutes the E C G was recorded before starting, and then at two, five, seven, and ten minutes Immediately afterwards pure oxygen was inhaled for one minute and the electrocardiogram was repeated it was recorded subsequently at five-minute intervals until the resting state was restored If the patient signalled discomfort or if obvious electrocardiographic changes appeared, the mixture was replaced by oxygen Levy's original criteria were used in interpreting the results, and a positive result was indicated by the presence of any of the following, alone or in combination the sum of the ST deviation in three standard leads and the chest lead totalling 3 mm or more, partial or complete reversal of the T wave in lead I with ST deviation of at least 1 mm , or complete T-wave reversal in the chest lead ST deviation was by far the most reliable change, occurring alone in 73% of 52 positive tests, and in combination in a further 23%, in 2 patients reversal of the T wave in the chest lead was found alone A positive result was obtained in 41 out of 43 patients in whom the test could be completed, and in whom a positive result might have been expected—a rate of 95% The test was completed in 5 out of 7 patients with intermittent claudication, and was positive in 3 no positive results were obtained in the controls, but the test was positive in 1 patient with suspected Stokes-Adams attacks without chest pain An exercise test, according to the method of Wood et al,[7] was also performed in 11 patients and the results agreed with those of the anoxia test in all except 1, in whom the anoxia test was positive and the exercise test negative the reverse was not encountered

Coulshed concludes that Malmstrom's modification of the anoxia test is satisfactory in that the results are comparable with those of the exercise test It has the advantage that it can be applied to patients incapable of exertion, and the patient is under continuous electrocardiographic control, but it clearly has disadvantages an anæsthetic machine or similar device and a supply of gases is needed in addition to the electrocardiograph, and the test takes considerably longer, there is also a greater likelihood of undesirable reactions, apart from anginal pain, and Coulshed had to abandon 25 out of 126 tests, usually owing to fear or dyspnœa

The limitations of all such tests must be recognised a negative result does not exclude angina pectoris or ischæmic heart-disease, but a positive result should make the physician very chary of discarding the diagnosis of angina if there are any clinical grounds for accepting it

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Prof JOHN FULTON, who had held chairs of physiology and of history of medicine at Yale University, died on May 29 at his home in Connecticut

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[2] *ibid* April 2, 1960, p 761
[3] Biorck G *Amer Heart J* 1946, 32, 689
[4] Larsen K H *Acta med scand* 1936, suppl 78, p 141
[5] Levy, R L, Williams, N E, Bruenn, H G, Carr, H A *Amer Heart J* 1941, 21, 634
[6] Biorck G *Brit Heart J* 1946, 8, 17
[7] Master, A M, Friedman, R, Dack, S *Amer Heart J* 1942, 24, 777
[8] Master A M *Bull St Francis San* 1953, 10, 1
[9] Wood, P, McGregor, M, Magidson, O, Whittaker W *Brit Heart J* 1950 12, 363
[10] Coulshed, N *ibid* 1960, 22, 79
[11] Malmstrom G *Acta med scand* 1947, suppl 195

Public Health

UNEVEN DISTRIBUTION OF CANCER IN WEST DEVON

WITH PARTICULAR REFERENCE TO THE DIVERS WATER-SUPPLIES

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The mortality from cancer in West Devon, on a twenty years' average, is 16 5% of the total deaths in the area In the nearby city of Plymouth the corresponding figure is 16 3%, and that for England and Wales stands at 16 8% On their face value these figures seem so closely related that no special inquiry would be indicated, but local " folklore " has it that certain parts of West Devon are rife with cancer To see whether there was any truth in this belief a pilot survey of deaths in the parishes bordering the river Tamar was made, and it at once became evident that a truly odd distribution did indeed exist, and a full-scale investigation of the whole of this area of West Devon was therefore undertaken

The inquiry was based on the local register of deaths as certified by the doctor who issued the certificate In the records there occurred, during the interval under survey, 5547 deaths, of which 787 were attributable to cancer The primary cause, say bronchopneumonia, was ignored if cancer of some organ (e g , stomach) was mentioned as contributory

The inclination of doctors to certify cancer has also been investigated, and it was found that where the incidence was away from the average there it remained, whichever doctor wrote the certificate.

Deaths by Parishes

From a preliminary analysis of the death register it was obvious that cancer was not evenly distributed A complete analysis of the records was therefore undertaken parish by parish (table I)

Table I includes the market town of Tavistock and 25 rural parishes, with their inhabitants The average death-rate from all causes is 12 1, but there is a considerable variation from parish to parish, which is undoubtedly to some extent conditioned by the extreme variations in population

TABLE I—INCIDENCE OF CANCER BY PARISHES
COMPARATIVE DEATH-RATES PER 1000 LIVING 1939–58

Parish	Population	Death-rate from *all causes*	Death-rate from *cancer* only	Death-rate *without cancer*
Tavistock Urban	5889	15 2	2 3	12·9
Bere Ferrers	2054	14 3	3 2	11 1
Bradstone	71	15 2	1 5	13 7
Brentor	481	15 5	2 2	13 3
Buckland Monachorum	2686	12 3	1 8	10 5
Coryton	139	9·4	0·4	9·0
Dunterton	52	11 4	2·6	8 8
Horrabridge	1232	12 7	2 3	10·4
Kelly	155	8 7	0·9	7 8
Lamerton	559	13·4	1 7	11 7
Lewtrenchard	185	11 8	1 8	10·0
Lifton	880	13·6	1·9	11 7
Lydford	2071	7 3	1 2	6 1
Marystowe	243	7 1	1 8	5 3
Mary Tavy	753	13·9	1·9	12·0
Meavy	447	15 1	2 8	12 3
Milton Abbot	659	12·9	1·6	11 3
Peter Tavy	344	11 1	2 2	8·9
Sampford Spiney	120	14 7	6·9	7 8
Sheepstor	76	13·9	3 1	10 8
Stowford	277	12·9	2 7	10 2
Sydenham Damerel	235	16 3	3 7	12·6
Tavistock Hamlets	821	11·5	2 7	8 8
Thrushelton	252	6·9	0·7	6 2
Walkhampton	557	9·0	1·5	7·5
Whitchurch	919	7·5	1 2	6·3
Averages		12 1	2 2	9·9

The death-rate from cancer, however, which has been standardised in column 4 of table I, does show a very remarkable variation. For example, the two large parishes of Bere Ferrers and Lydford have each a population of over 2000, but the death-rate for Bere Ferrers is 3 2 and that of Lydford 1 2, a difference of $2^{1}/_{2}$ times, and this on a twenty years' average Sampford Spiney, which is a black spot, is more than twice this again These figures strike an obvious discord with the average death-rate of 2 2 per 1000 living, and there is very little difference between this figure and that supplied by the Ministry of Health for England and Wales of 2 01 per 1000 living But it is clear that considerable differences do in fact occur from parish to parish

Table II gives the total number of deaths by parishes, with the associated deaths from cancer and the percentages of cancer deaths among total deaths There is again a great variation in the percentages of cancer deaths to all other deaths, and, taking parishes with a reasonable population, the remarkable fact emerges that a parish like Bere Ferrers has a cancer mortality of 22%, whereas the adjoining parish of Buckland Monachorum, with a comparable population, has only 14%

TABLE II—DEATHS BY PARISHES, 1939–58

Parish	Total no of deaths 1939–58	Deaths from *cancer* only	Percentage of cancer to all deaths
Tavistock Urban	1526	229	15 0
Bere Ferrers	480	107	22 3
Bradstone	20	2	10·0
Brentor	126	18	14 3
Buckland Monachorum	560	80	14 3
Coryton	22	1	4 5
Dunterton	13	3	23 0
Horrabridge	265	48	18 1
Kelly	18	2	11 1
Lamerton	127	16	12 6
Lewtrenchard	40	6	15 0
Lifton	201	28	13 9
Lydford	268	45	16 8
Marystowe	28	7	25 0
Mary Tavy	170	23	13 5
Meavy	107	20	18 7
Milton Abbot	144	18	12 5
Peter Tavy	67	13	19·4
Sampford Spiney	30	14	46 7
Sheeptor	18	4	22 2
Stowford	62	13	21 0
Sydenham Damerel	63	14	22 2
Tavistock Hamlets	168	40	23 8
Thrushelton	30	3	10·0
Walkhampton	90	15	16 7
Whitchurch	117	18	15 4
Totals	4760	787	16 5

Table III shows that those who succumb to cancer have, on an average, four years less expectation of life than those who succumb to all other disorders This point is not emphasised at the moment, but it will be suggested later that an active and discoverable cause of the disease is present among the community

Having investigated the cancer incidence in a general statistical way, which did not yield any really positive result, except those set out in the above tables, the situation was plotted on a map The 5547 deaths were depicted on a 6 in to the mile Ordnance Survey map Deaths from cancer were marked by a cross, and those from other diseases by a circle The extraordinary distribution of the disease at once became apparent For example, in one hamlet the ratio of crosses to circles is 1 in 12, whilst in an adjoining hamlet of comparable community the ratio is 1 in 3

Geology

A rough geological map of the area is shown in fig 1 The remarkable distribution of cancer is mainly confined to the southern part. The black areas represent districts of high cancer mortality and the light areas those where the incidence of the disease is considerably below average

TABLE III—AVERAGE AGE OF DEATH (IN YEARS) BY PARISHES 1939–58

Parish	Average age of death from *all causes*	Average age of death from *cancer* only	Average age of death *without cancer*
Tavistock Urban	73·4	68·9	74·1
Bere Ferrers	73·6	71·0	74·3
Bradstone	74·0	85·0	72·7
Brentor	74·0	69·4	74·1
Buckland Monachorum	74·0	70·4	74·6
Coryton	77·0	67·5	77·5
Dunterton	72·1	62·5	75·0
Horrabridge	72·8	68·6	73·8
Kelly	69·2	69·7	69·1
Lamerton	73·1	66·0	74·7
Lewtrenchard	70·6	70·8	70·6
Lifton	72·2	68·0	72·8
Lydford	71·4	66·0	72·5
Marystowe	72·6	70·4	73·4
Mary Tavy	72·6	68·7	73·2
Meavy	74·2	73·7	74·3
Milton Abbot	74·0	71·9	74·3
Peter Tavy	69·1	66·5	69·8
Sampford Spiney	72·6	69·0	75·6
Sheeptor	73·8	73·8	73·5
Stowford	76·9	77·5	76·7
Sydenham Damerel	74·6	73·2	75·0
Tavistock Hamlets	71·2	65·0	73·0
Thrushelton	71·7	69·2	71·9
Walkhampton	73·1	67·8	74·1
Whitchurch	73·7	68·1	74·8
Average	73·0	69·9	73·7

The surface of the area is covered by four formations which rate in geological time (1) devonian (the oldest), (2) lower carboniferous, (3) granite intrusion, (4) new red sandstone

Devonian—This is a sedimentary deposit and consists of shale, grits, and limestones, which has, during the course of time, become very highly mineralised Both common and rare minerals have been gleaned from this area from time immemorial

Carboniferous system—This also consists, in the main, of shale, grits, and limestones, but differs greatly from the former formation in not being mineralised

Granite system—This is an intrusion of igneous matter into the two former systems and is highly mineralised, but not to the extent of the Devonian stratum

New red sandstone—This is a band of coarse deposits and the people living thereon are not included in this paper

Table IV shows that the percentages of deaths from cancer on the two highly mineralised strata are significantly higher than those on the carboniferous and the new red sandstone series Where the percentage of cancer is greatest so the average age of death is proportionately diminished This table is, in some respects, misleading, for the figures can be worked only on a parochial basis and make no allowance for the hamlets contained therein which have a greater or a smaller percentage than that of the average for the parish as a whole

In fig 1 the devonian stratum has many black spots in it They represent small villages or hamlets, with populations between 200 and 500 Adjacent to them are white spots—hamlets where cancer is relatively rare (in three cases, non-existent) On the other hand, in the carboniferous stratum there are no black spots, but there are some places where the disease is non-existent The same applies to the white spot in the middle of the granite area at Post Bridge, which is also free of the disease The records of the Superintendent Registrar reveal that these conditions have not varied for roughly two generations

Statistical Approach

The grouping of cancer incidence on the large-scale map showed a distinctived pattern and when it was transferred to the geological survey the pattern seemed to be restricted to one geological formation—devonian

A series of two-fold correlations were then undertaken as follows

	r	Standard error (S.E.)
(1) Between cancer of the stomach and cancer of all other sites on the *devonian* stratum	+0·4972	±0·153
(2) Between cancer of the stomach and cancer of all other sites on the *carboniferous* stratum	+0·0843	±0·193
(3) Between cancer of the stomach and cancer of the breast in parishes on the *devonian* stratum	+0·2319	±0·189
(4) Between cancer of the stomach and cancer of the breast in parishes on the *carboniferous* stratum	+0·0235	±0·237
(5) Between cancer of the lung and cancer of the stomach in parishes with the highest incidence of cancer (over 90% devonian)	+0·4084	±0·195

There is an indisputable difference in the correlations between cancer of the various sites on the carboniferous and the highly mineralised devonian strata For example, correlation between cancer of the stomach and cancer of all other sites on the devonian stratum gives a positive $r = +0{\cdot}4972$ with S.E. ±0·153, which is a significant association On the other hand, a similar correlation between cancer of the stomach and cancer of all other sites on the carboniferous stratum gives $r = +0{\cdot}0843$ with S.E. ±0·193 This discrepancy is also apparent in the correlation between cancer of the stomach and cancer of the breast on these two strata *It is also significant that* $r = +0{\cdot}4083$ with a S.E. ±0·195 in a correlation between cancer of the lung and cancer of the stomach in those parishes with the highest incidence of cancer (these consist of over 90% devonian stratum)

These correlations are in the nature of a controlled experiment in which all possible variables would be eliminated, and the inference is that some cancer-provoking agent is more active in one area than in the other It is suggested that this agent is a trace element occurring in sufficient concentration on the devonian stratum to be capable of detection

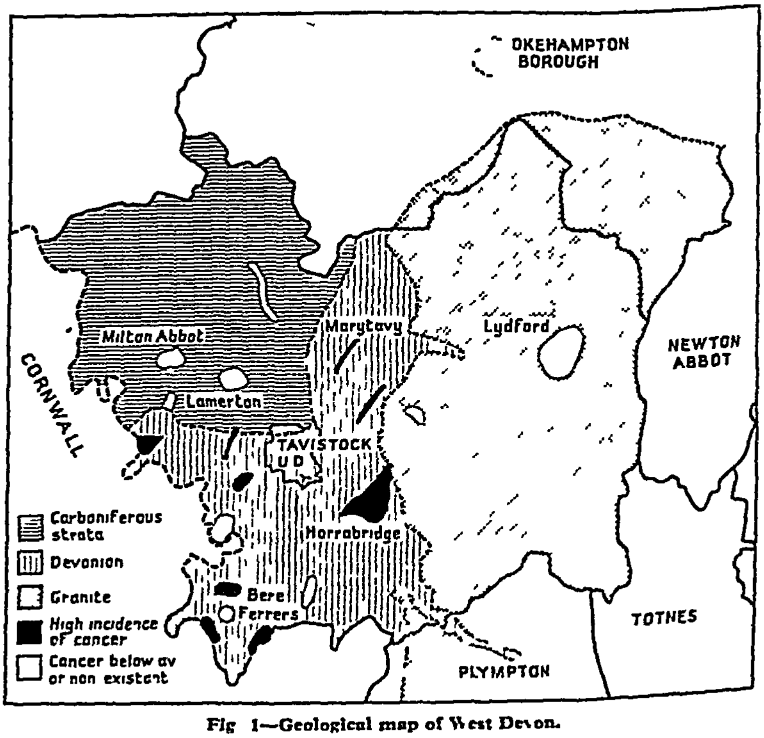

Fig 1—Geological map of West Devon.

TABLE IV—DISTRIBUTION OF DEATHS ON THE VARIOUS GEOLOGICAL STRATA

—	Granite	Devonian	Carboniferous	New red sandstone
Total no of deaths 1939–58 inclusive	473	2048	1046	388
Total no of deaths from *cancer only*	99	374	148	56
Percentage of *cancer* to *all other deaths*	20·9	18·3	14·1	14·4
Average age of death from *all causes*	75·6	71·6	71·7	73·6
Average age of death from *cancer* only	66·3	68·0	69·8	66·1
Average age of death *without cancer*	78·1	72·4	72·0	74·9

Incidence of Cancer in relation to Water-supplies

All attempts to find a common factor which might be affecting the incidence of cancer failed—apart from a study of water-supplies

The water-supplies of the area come from two sources (1) underground supplies from wells and springs, and (2) upland surface supplies from the moorland water which has been impounded in reservoirs (but these are not pure surface waters, since there is a continuous seepage into them from the broken-down mineralised granite)

The parishes with the highest incidence of cancer, and the highest death-rate, derive their water-supplies from wells and springs, which, with two exceptions, are all on the highly mineralised strata, devonian or granite The converse obtains in the parishes with a low incidence of cancer, where, generally speaking, the water-supply is derived from the non-mineralised stratum

Percentage of Cancer to Other Deaths

Parishes with high incidence of cancer		
Sampford Spiney	46·7%	Springs
Marystowe	25·0%	Wells
Tavistock Hamlets	23·8%	Wells
Dunterton	23·1%	Wells
Bere Ferrers	22·3%	Springs
Sydenham Damerel	22·2%	Wells
Sheeptor	22·2%	Springs
Stowford	20·9%	Wells

Parishes with low incidence of cancer		
Coryton	4·5%	Wells
Bradstone	10·0%	Wells
Thrushelton	10·0%	Wells
Kelly	11·1%	Wells
Milton Abbot	12·5%	Springs
Lamerton	12·6%	Springs and wells
Mary Tavy	13·5%	Piped from moor
Lifton	13·8%	Springs, piped

Cancer Death-rate per 1000 Living

Parishes with highest death rate from cancer		
Sampford Spiney	6·9	Devonian
Sydenham Damerel	3·7	Devonian
Bere Ferrers	3·2	Devonian
Sheeptor	3·1	Granite
Meavy	2·8	Devonian
Tavistock Hamlets	2·7	Devonian
Stowford	2·7	Carboniferous
Dunterton	2·6	Carboniferous

Parishes with lowest death-rate from cancer		
Coryton	0·4	Carboniferous
Thrushelton	0·7	Carboniferous
Kelly	0·9	Carboniferous
Whitchurch	1·2	Devonian
Lydford	1·2	Granite
Walkhampton	1·5	Devonian
Bradstone	1·5	Carboniferous
Milton Abbot	1·6	Carboniferous

It is necessary to discuss a few exceptional cases

First, the parish of Bere Ferrers, on the south of the devonian stratum here the average mortality from cancer is 22·3%, with black spots reaching up to 41% Nevertheless, in the midst lies the hamlet of Cotts, where the average age of death of the population is over 80 years, and where no deaths from cancer have ever occurred according to the records of the Superintendent Registrar

Slightly north of this is the large hamlet of Morwellham, which during this measurable period has only had 1 case of cancer, and that was imported

Eastwards is the large parish of Buckland Monachorum, made up of several hamlets—Yelverton, Crapstone, Buckland village, Clearbrook, and the very large hamlet of Milton Combe The whole parish, apart from Milton Combe, has been supplied with upland surface water by Plymouth Corporation, and has an identical cancer mortality to that of the city On the other hand Milton Combe derives its supply from a perpetual spring in the high reaches of the village, and here we have a cancer mortality of 6·2%, as against that for the parish as a whole of over 15%

On the carboniferous and granite areas there are no exceptionally high spots of cancer incidence, although there are several small areas where the occurrence is considerably below the average for the area as a whole

The most exceptional area of all is the parish of Sampford Spiney, and part of the parish of Horrabridge which lies north of the river Walkham, marked as a triangular black patch in fig 1 The percentage of deaths from cancer in Sampford Spiney parish reaches the extraordinary level of 46%, and there is one stretch lying parallel with the river where the percentage reaches 66% This, as far as can be discovered, is the highest percentage of cancer mortality on record anywhere.

Horrabridge is a compact village of about 1200 people For many years it has been an ecclesiastical unit, but was not until recently amalgamated into a civil parish Before this it had, for administrative purposes, been governed by four parishes (Sampford Spiney, Walkhampton, Whitchurch and Buckland Monachorum), and in consequence has three separate water-supplies The area of Horrabridge which derives its water from Watery Ford, which is in the parish of Sampford Spiney, has a cancer mortality of 46% (this is identical with the mortality for Sampford Spiney parish as a whole) The intermediary part, which was in the parish of Walkhampton, is supplied by springs from what is known as the Chipple Park supply, and has a cancer mortality of 8% The south-western part, which was in the parish of Buckland Monachorum, has for a number of years been supplied by Plymouth Corporation

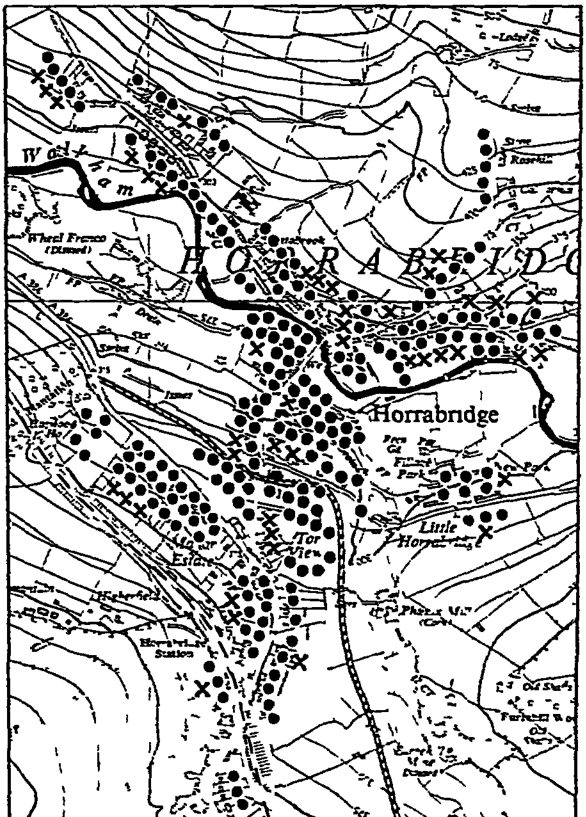

Fig 2—Distribution of deaths from cancer (X) and deaths from other causes (●) in Horrabridge The areas of the three different water-supplies are separated by the River Walkham (black) and by the hatched line (see text for fuller explanation) This map is based on the Ordnance Survey National Grid (Crown copyright reserved)

with upland surface water from Dartmoor, and has an identical cancer mortality with the rest of the parish of Buckland Monachorum, and that of Plymouth city itself

Fig 2, showing the distribution of deaths from cancer and from other causes in Horrabridge, is diagrammatic and has had to be reduced from the 24 in. to the mile Ordnance Survey map On this larger scale the individual houses and their water-supply appeared in distinctive colour, with the cancer and other deaths It is not possible to convert this colour presentation to black-and-white symbols and still maintain complete accuracy For example, the line of demarcation between the sectors is too sharp and makes no allowance for infiltration of the Plymouth water-supply to the south-west and the Watery Ford supply to the north-east But fig 2 does show the remarkable number of crosses representing cancer which lie to the north of the River Walkham

The distribution of cancer in this compact community of Horrabridge, which in the radius of half a mile has three distinct mortality-rates, cannot be explained by any current theory Here there is a homogeneous group, following the same occupations, eating the same food, and in an identical environment, and merely separated one from another by the natural boundaries of the river Walkham, which is crossed by a bridge Here, for generations, the people have intermarried freely, and their social activities have been combined, yet each artificial section of the community has a widely different cancer mortality As far as can be assessed the only difference that could account for this is in their water-supply

Discussion

Certain facts support the hypothesis that cancer in this area is indissolubly connected with water-supplies the distribution is beyond dispute, being derived from the actual death certificates, the geological formations are unquestionable, and the visual and statistical evidence for the distribution, as recorded in maps and tables, cannot be questioned

Stocks [1] *stated*

> "Apart from these social and climatological factors, another obvious difference between towns which might conceivably affect cancer rates to a pronounced extent is their water supply, which may be drawn from very divers kinds of sources *In recent years very* potent effects on metabolism of minute quantities of elements such as fluorine and manganese which would not be easily detectable in water supplies, have been revealed "

I suggest the alternative or supplementary possibility that the radioactivity of the water may be a factor of importance This is clearly a difficult subject requiring careful and detailed investigation and critical assessment A survey of the radioactivity of these water-supplies has been started in collaboration with Dr J D Abbatt Meanwhile a great deal of work must be done before any conclusion can be reached about the causative factors involved

Summary

(1) Analysis of the death records for a period of twenty years shows an extraordinary sporadic distribution of cancer in West Devon

(2) This sporadic distribution is restricted to the highly mineralised devonian stratum and does not appear on the adjacent carboniferous or granite formations

(3) Areas of very high and very low incidence of the disease appear to be inextricably related to their water-supplies

(4) There may be a cancer-provoking ingredient in these water-supplies which could be isolated by micro-chemical examination

For help in the preparation of this paper, my thanks are cordially accorded to Prof J S Mitchell, F R S, of Cambridge I must not allow this opportunity to pass without thanking my secretary, Miss P B Fletcher, without whose enterprise and endurance this research would not have been possible

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[1] Stocks, P Regional and Local Differences in Cancer Death Rates H M Stationery Office, 1947

Registration of Stillbirths

In an annotation last week on the Sex Ratio of Stillbirths (p 1179) we applauded the practice in Scotland of requiring those registering stillbirths to state on the certificate the cause of death, and regretted that this practice is not followed in England and Wales We should have added that this defect is soon to be remedied Under the Population (Statistics) Bill,[1] which is awaiting the Royal Assent, certificates for registration of stillbirths in England and Wales will, as in Scotland, include the cause of death The Bill also calls for inclusion in such certificates (in England, Wales, and Scotland) of the estimated duration of the pregnancy

Occasional Book

MEDICINE VERSUS MORALS

A Reply to a Sociologist

Lady Wootton, the eminent sociologist and one of the most penetrating minds we have, has added to her stature with a remarkable book [2]

This monumental work draws together a mass of statistical records and published work relating to socially undesirable behaviour, places it in critical perspective, and devastates most of the theories that have grown up to account for it, saying firmly "Thus far we have come, and no further" doctors and social workers bear the brunt of the attack She writes with an economy of language and turn of phrase that make much of it a delight to read, and surely equivalent in the ground it covers to the customary sociological treatises (especially translantic ones) of three times the size Lady Wootton does little to penetrate the mists that lie ahead, but this is perhaps too much to expect from one so cautious in approach

SHATTERED BELIEFS

Taking as the subject of her thesis "those actions on the prevention of which public money is spent", she leaves a number of cherished beliefs in pieces Divorce, for example, widely held to be an increasing problem, is shown on close examination to have more than halved between 1947 and 1955, and even in the U S A the proportion of broken marriages has been on the decline since the beginning of the century, taking account of such factors as greater longevity In comparison, illegitimacy is a numerically greater problem, with about 1 live birth in 3 conceived extramaritally in this country, though most of the children come to enjoy a fairly normal family life But above both towers the figure for lawbreaking, with over $^{3}/_{4}$ million found guilty in criminal courts in England and Wales during 1955 Why, Lady Wootton asks, do men seem 7 times more criminal than women, and why has so little work been done to explain this remarkable fact? The typical criminal of today, she points out, is the motorist, for about half of the total were motoring offences, 50,000 or so of them for hazardous driving of some kind, and a further 90,000 for speeding—figures which alter the impact of those for breaking and entering (7881 for equivalent ages) or larceny (45,101) Sexual and violent crimes were even fewer than these The "delinquent driver" is one of the problems of the time, as the mounting toll of road deaths shows, and Lady Wootton points accusingly at the class-linked moral standards which hold this dangerous and antisocial behaviour as of such small account Class bias is shown, for example, in sentencing policy, about half those guilty of the desperate crime of begging are sent to jail, against less than 13% of drunken and 31% of dangerous drivers We can indeed ask whether there is any valid qualitative difference between a "carve-up among the Teds" and the great range of deviant behaviour exhibited by the average rugby-football club, which starts its activities with the scrum (assault, and even grievous bodily harm), goes on to the communal bath (indecent exposure), the enormous consumption of beer (drunken and disorderly behaviour), and the singing of songs (obscene language), and ends on the way home with the collection of inn-signs, road-names, and bus-stops (larceny) Both forms of delinquency may or may not involve third parties, and the fact that one does so more than the other may well be due to an unfair weighting of social opprobrium, plus the unfair availability of semi-private premises Lady Wootton does not list what might be called examples of upper-class viciousness—from Stock Exchange floor to blood sport

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[1] See *Lancet*, 1959, ii 976, *ibid* Feb 6, 1960, p 340

[2] *Social Science and Social Pathology* By BARBARA WOOTTON, Baroness Wootton of Abinger, assisted by Vera G Seal and Rosalind Chambers London Allen & Unwin 1959 Pp 400 35s

Those who believe that the Welfare State has rotted man's will to work may be surprised by the observation that, with a working population of $23^1/_2$ million, only 7000 of the idle were judged by the National Assistance Board to be capable of work if they really wanted it, and the recalcitrant fraction was even smaller, for only 49 people were convicted of persistent refusal to work in 1955 Lady Wootton is at her best in exposing deficiencies in the Welfare State, which does not seem to be faring as well for the needy as many like to think "Problem families", however, are much too easily dismissed as sociogenic Bernard Shaw may have been on fairly sure ground when, 60 years ago, he alleged that the only thing wrong with the poor was their poverty, but the bottom rungs of today's social ladder are surely much occupied by persons gravely handicapped by defects of intellect or personality, whether of genetic origin or not The need for precise data on the matter is clear, and even Dr J A Scott's large survey[3] falls short of valid criteria for such disturbance, though the perpetuation of "problem status" is strongly suggested by the fact that like tends to marry like, judged by intelligence, personality, and temperament[4] Nor can it be doubted that neurotic, but above all personality difficulties figure largely among the persistently unemployed[5] The difficulties of measuring behaviour of the kind exhibited by the "submerged tenth" and of securing the cooperation of these elusive subjects for testing must not blind us to their obvious disabilities There is indeed a quaint 19th-century Fabian flavour to some of Lady Wootton's opinions, though she retracts from the view that poverty causes stealing, pointing out that, if anything, lack of money seems to be correlated with honesty

CAUSES OF ANTISOCIAL BEHAVIOUR

Delinquency, as a class-linked phenomenon, may, as Lady Wootton points out, be perfectly "normal" in its context, and psychodynamic views of the significance of stealing, &c, be somewhat redundant Differences in social class, however, have been demonstrated with regard to psychiatric illness, which, in the lowest stratum, is much more readily manifested in violent and antisocial ways[6] Moreover, the impressive work of Stott[7] (a sociologist, let it be noted) has shown evidence of wide fields of behaviour disturbance in a majority of what might be termed "sub-cultural offenders" in Glasgow The McCords (also sociologists), in their very valuable work,[8] confirm the growing belief that the "neighbourhood" matters far less in crime than the family relationships of the people that happen to live there Certainly one can agree with Lady Wootton that to regard crime as a "thing in itself" (like flat-feet, one might say) is false, and this notion is the source of much wasted effort in research Deviant behaviour appears in many forms and in many settings, and her nihilistic views on the value of past researches into causes of crime (amplified in this book) are well known It seems that "idiopathic" antisocial activity, like idiopathic epilepsy, is slowly being whittled away, as, for example, by the recent association of a type of delinquency with schizophrenia in adult life,[9] and with cerebral (especially temporal-lobe) damage

One can, perhaps, delineate three main areas of research into the origins of antisocial behaviour Firstly, the genetic, which Lady Wootton as a sociologist does not touch, although had she looked into the conflicting results of some twin studies her views of them would probably have been no less severe than of everything else Secondly, there are the first five formative years of life, long the stamping-ground of psychoanalysts but increasingly the province of other more strictly scientific researchers And finally there is the long period of adolescence, beloved of sociologists, where antisocial behaviour makes its appearance and climbs steeply to a summit at 14–17 This is the "easy" period to work with, for one knows approximately who is delinquent and can approach them almost as if they were adults with questionnaires, &c It is, broadly speaking, this period of research (or even later) which receives so much cold water from Lady Wootton, though to those who believe that personality traits are formed much earlier, it comes as no surprise when such factors as religious observance, youth clubs, and school reports show a rather tenuous relationship to delinquency

It is doubtful how far research into cause at this stage is helpful, for it may well be that correlations elucidated between behaviour and parental attitude—for example, those of Nye[10]—are meaningful only as far as they reflect earlier traits which persist to some degree Indeed the much more valid work of the McCords,[8] (confirming many of the Gluecks' previous findings[11]) shows the great importance of early home factors, particularly cohesiveness, parental love, and consistent discipline Circumstances in youth can, without doubt, alter for good or ill a lad's chance of offending, but if the weight of clinical experience, together with the studies I have quoted, mean anything, then the concepts of accident and contamination must, in very many cases anyway, give way to more basic factors Lady Wootton makes the important point that one of the most promising leads in criminology is the success of the prediction scales based on sociological factors—for example, that of Mannheim and Wilkins[12] Their valuable prediction guides for further offending, however, such as drunkenness, recidivism, occupation instability, and living away from parents, could hardly be more closely related to those very inadequacies which one expects to find in the persistently antisocial Surely all have a common origin

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[3] Scott, J A *Lancet*, 1958, i 204
[4] Slater, E., Woodside, M Patterns of Marriage London, 1951
[5] Markowe M, Tonge, W L, Barber, L E D *Brit J prev soc Med* 1955, 9, 39
[6] Myers, J K., Roberts B H Family and Class Dynamics in Mental Illness, pp 222 et seq New York and London, 1959
[7] Stott D H *The Howard Journal*, 1959, 10, 67 See also *Lancet*, 1958, ii, 1054
[8] McCord W McCord, J Origins of Crime New York 1959
[9] O'Neal P, Robins L N See *Lancet* Jan 23 1960, p 216
[10] Nye F I Family Relationships and Delinquent Behaviour New York and London 1958
[11] Glueck, S, Glueck, E T Unraveling Juvenile Delinquency Cambridge, Mass 1950

PSYCHOANALYSIS AND THE SOCIAL WORKER

Lady Wootton's attitude towards psychiatric and other social workers is given at length, but it seems oversimplified Many social workers do neglect the material and social side of their work in favour of the dynamic—treating people is interesting—and Lady Wootton is joined by a senior psychoanalyst[13] in criticising social workers who practise as half-baked analytic therapists with the words " client " substituted for " patient " and " case work " for " psychotherapy " (46% of social workers in 290 clinics in the U S A, we may recall, admitted to practising psychotherapy[14]) Nevertheless, to concede, as one surely must, that personality factors contribute to social distress is to admit the need for social workers to have some knowledge of psychiatry and expertise in turning that knowledge to good use Granted that genuine accidental hardship does still arise, yet material help, naïvely given, is of limited value to certain people indeed it may block the inadequate person from the necessary mobilisation of his own resources

Concerning psychoanalytical theory, Lady Wootton may be right to pass it by on the other side, using as an excuse that very unsatisfactory dictum of some psychoanalysts that only the fully analysed can understand it Personal analysis may be necessary for the fullest belief, but the uninitiated can readily grasp the basic theory This is important, for the various schools of analytic psychiatry are unique in presenting some sort of framework of hypotheses to account for forms of undesirable activities which are far too complex for socio-economic theory to grapple with Why, for example, did Mr A expose himself in public at that time to that person? Why did young B only steal from offertory boxes in churches? Why did prisoners C and D go over the wall a few days before their release was due, and why did cat-burglar E make that trivial but obvious error that made it certain he would be caught and punished? Endless instances can be quoted of cases, simple and complex, where the seemingly inexplicable is found to fit into a uniform framework of theory Let us agree that hypotheses are only hypotheses, and very few among psychiatrists would hold that any school of psychiatry holds the key to ætiology, prevention, and cure, nor do they wish to take over the prison service, though perhaps too many psychiatrists overreach their facts in putting forward a point of view The astute psychiatrist, drawing on library and consulting-room, is well placed to understand people, but he could (especially if strait-jacketed by dogma) understand them less than an exceptional schoolmaster, novelist, or even policeman might do Psychoanalytic thought, however, is mingling more and more with sociological research (what are an infant's relations with his parents if not social?), and interdisciplinary studies, especially in the U S A, are adding valuable knowledge This approach cannot be neglected by anyone who wishes to understand the origins of crime

The one topic closely related to psychoanalytic theory on which Lady Wootton does embark is that of maternal deprivation in relation to later antisocial behaviour Here, after roundly (and fairly) condemning earlier dogmatic assertions, she ends

> " Up to the present, therefore, research into the effects of maternal deprivation is to be valued chiefly for its incidental exposure of the prevalence of deplorable patterns of institutional upbringing, and of the crass indifference of certain hospitals to childish sensitivities Without doubt this research has already had excellent practical effects in stimulating many of the authorities responsible for children's homes and hospitals to change their ways for the better Meanwhile, it is clear that, where the old bad methods survive, the children, as one would expect, suffer according to their temperaments and circumstances in various ways and in various degrees *Now and again their deprivation seems to express itself in a well-marked pattern of indifference to everybody except themselves, of which one of the expressions is repeated stealing More than this, however, we cannot say* " (The italics are not the author's)

She seems to have said enough, however, in this excellent summary to place her on common ground with Dr Bowlby—to her surprise perhaps

LADY WOOTTON AND THE DOCTORS

The somewhat ambivalent attitude towards doctors which Lady Wootton shows on some issues may have tilted her usual impartiality here and there Doctors, as rather obvious parent-figures, are accustomed to respect, and this, let it be acknowledged, they get from Lady Wootton in good measure with regard to the humanising effects of medical theories on forensic attitudes Doctors are also familiar with the inevitable negative feelings (reflecting a Shavian distrust doubtless), though perhaps Lady Wootton goes rather far in the auspicious terminal paragraphs of her Conclusions

> " In part, the prevailing emphasis upon the medical element in anti-social behaviour must be seen as an expression of the unique prestige enjoyed today by the medical profession This materialistic age, unable to look with confidence beyond the grave and believing the doctor to hold the keys of life and death, has invested him with the respect and awe once associated with the priesthood The doctor, like father, knows best, and his prestige is expressed in many ways The doctor, unlike the teacher or lawyer, is customarily addressed reverentially by the title of his profession In the courts the doctor's time, unlike that of most other witnesses or of jurors, is assumed to be so valuable, that procedure must be adjusted to take account of this his evidence must be taken early, and he must if possible be released immediately that it has been given And, although even now doctors do not automatically get all the pay they ask for, it is significant that since the war and in defiance of long-standing tradition of equality, the salaries of medical staffs in universities are now always higher than, and sometimes more than twice as high as, those of their colleagues in other faculties "

This alleged attitude has, she believes, biased all researches to the disadvantage of sociology, but her suggestion that research-workers in medicine rival their colleagues in atomic physics in attracting funds is sadly out, with a mere £3 million odd for the whole M R C budget—and anyway is this attitude true? University salaries doubtless reflect length of training and outside attractions, and the accommodating attitude of the courts (which not all of us have noted) surely reflects respect for sick people rather than for the doctor Barristers and business men often sit in judgment upon medical matters, but never have doctors the opportunity to chair a Royal Commission on anyone else, nor is medicine helpful in politics or the other callings between which, at top levels, one can filter laterally

Psychiatrists, the subjects of her thesis, enjoy the lowest prestige in honours, training, research funds, ment awards, and everything except potential To take one or two examples of apparent bias, she seems particularly amazed at the "extravagant claims" of Dr Stafford-Clark that a psychiatrist can understand a person "after a few interviews" better than the patient himself or his spouse But one does not need a D P M surely to realise how little people (especially ill people) understand themselves The shock at hearing one's recorded voice is probably no greater than the shock from self-realisation in other ways, and married couples are usually too involved to understand each other, man and wife is one flesh in more than a theological sense Her tentative suggestion that E E G abnormalities in delinquent groups may be written off as the result of their recent experiences disregards that satisfying though admittedly little understood correlation between neurophysiological and emotional immaturity Child-guidance clinics, she says, had to be " invented to deal with the misfits of the normal educational system", this being done " on the principle that it is easier to create a new institution than modify an existing one" There is much in this, but the view underemphasises the severity of many disorders of childhood and the ability of even a modified normal school to handle them Relations in the home far outweigh the school in importance, and guidance work with the parents is no less important than treatment of the child It is good, however, that educationally subnormal classes are seen more in ordinary schools

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[12] Mannheim H, Wilkins L T Prediction Methods in Relation to Borstal Training H M Stationery Office, 1955

[13] Glover E The Roots of Crime London, 1960

[14] Berkman T D Practice of Social Workers American Association of Psychiatric Social Workers 1953

Lady Wootton illustrates the increasing influence of psychiatric thought by the number of magistrates' referrals for psychiatric opinion, which rose from 2000 in 1927 to 4800 in 1955 If, however, we recall the rise in population between those dates and the increase in the number offending from 140 to 216 per 100,000 (from 1925 to 1955 for over 17s),[15] this figure of 4800 among the $^3/_4$ million lawbreakers seems, rather, to be solid evidence of magisterial inertia Classification of lads after sentence is another matter and far more use is made at this stage of psychiatric reports There are, however, few instances where her onslaught can be thus readily resisted, on our fruitless attempts to define mental health, defect, and psychopathic personality, for example, there is little to be said in defence

MENTAL HEALTH AND CRIMINAL RESPONSIBILITY

With these muted reservations in mind, one can approach the important chapter on concepts of mental health and disorder in relation to criminal responsibility —surely the gordian knot of psychiatry The decision in the Mental Health Act (1959) to define psychopathic behaviour in terms of "abnormally aggressive or seriously irresponsible conduct" cannot be expected to still dispute, and Lady Wootton (writing before the Act) makes short work of the tautology which defines a syndrome in terms of behaviour and then invokes that behaviour to justify the syndrome. To abandon the principles laid down in the McNaughten rules and admit to diminished responsibility elsewhere will, she believes, start us down the slope that ends in abandoning the concept of criminal responsibility altogether The person who is clearly suffering from psychiatric illness, however, even though not in the strict McNaughten sense, involves us in no great difficulty and it is hard to see how his exclusion from standard penal practice represents a significant step towards a slippery slope But in conditions where abnormality is judged only in terms of antisocial behaviour (the dreaded tautology) it is probably impossible to find acceptable definitions and "cut-off points" on the continuum between the "normal" and the occasional subcultural offender to the severely psychopathic recidivist

Few, if any, of us are entirely free of psychopathic traits, and further time spent arguing among ourselves about the meanings of words is, in the present state of knowledge, time wasted But the offenders exist in their thousands and cannot be ignored, be they never so difficult to define, so where do we go next? It is perhaps very significant that, as was noted recently,[16] the most advanced work of the Prison Commission (on the lay side and with very little medical help) resembles closely the current trends in administrative psychiatry with group methods, graded incentives, open doors, half-way houses, and even (for certain ages) day centres Therapeutic progress certainly need not wait upon ætiological fact, for surely a great part of our effective pharmacopœia was in empirical use for many years, and even now when we think we understand how liver cures pernicious anæmia we cannot comprehend why, in the first place, the vitamin-B_{12} deficiency arose in that person at that time

Application of our efforts towards the "cure" rather than the theoretically more desirable ætiological end has the added point that orthodox descriptive studies are of very limited value, and retrospective ones scientifically shaky A really fundamental and valid project would consist of little less than very detailed life-studies of a large random number of children who, by virtue of the inevitable interference, would no longer be random There are the further difficulties of vast expense and lapse of time, for conclusions could hardly be expected in less than a generation.

Work in other fields may be equally frustrating, for notwithstanding the interesting possibilities in schizophrenia and affective disorder it seems likely that not for many decades, if ever, will psychopathy be comprehensible in biochemical and pharmacological terms It can hardly be doubted that study of the treatment processes, both lay and medical, and their outcome is a priority, and one shudders to think what Lady Wootton will say when she examines in detail the claims implicit in the phrase in the Act "susceptible to treatment" What treatment? Has any of it really been shown to work? And if no effective treatment is known to exist, why create an Act to make it compulsory? But the trend is surely right, and it makes a change for legislation to run ahead of knowledge

Society need not fear that by throwing overboard the ideas of sin and retribution it opens the seacocks to unlimited lawlessness No-one knows the value of deterrence, and the history of capital-punishment reforms suggests that it is limited "Punishment", however, will remain implicit in the compulsory nature of the treatment process, with in serious cases, removal of the transgressor from his environment No-one has suggested that Society should not be protected from its dangerous members (both penal and therapeutic demands require the longer detention of the more dangerous) and a clinical orientation should indeed make the situation more secure

The study of penal and medical treatments raises some difficult practical issues, for one wishes that the Prison Commissioners were as imbued with the scientific approach as they are with courage and innovation Random allocation of men to such new projects as open prisons, group counselling, or the boarding-out hostel would readily give valuable information, and the Home Office rule on follow-up of discharged men must be relaxed (automatically perhaps with wider use of after-care) The rights of the transgressor may be whittled away slightly by scientific control, but public opinion may not be far from accepting such necessary conditions for acquiring knowledge Scarcely a sensational crime is reported without some newspaper demanding that the offender be handed over for "scientific tests", and though we have not yet the tools to do much with the individual case, the attitude shows that people are not wholly averse to throwing our criminals to the scientists, whatever their mixed motives may be Medical ethics are a not unreasonable guide here, for doctors believe it justifiable to use a treatment experimentally where its value is still in doubt, and by this token the prisons need have no qualms, for a colossal question-mark hangs over the effectiveness of the penal services

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[15] Pakenham, Lord. Causes of Crime, p 28 London, 1958

[16] *Lancet*, 1959, ii 1015

The medical profession is as much at fault as the penal authority in this neglect of basic research What have we to show for all the work put in over the years at Belmont psychopathic unit, for example, or Duncroft approved school, or the psychotherapy at Wormwood Scrubs? We do not know what sorts of effects different types of treatment have on which kinds of patients

Quite what Lady Wootton believes herself on this issue of freewill and responsibility is not clear She admits that to abandon these concepts would solve a lot of problems, but her biting exposure of conflicting and inadequate medical testimony make it plain that she has great doubts, to say the least, about the medical approach Her more recent views are very important Thus, in the House of Lords discussion of the Act last June, she pointed to the "profound and far-reaching revolution" implicit in section 4, but added that she was quite prepared to embark upon this road[17] In August she faced the prospect of discarding "guilt" and concluded that, though drastically different, a diagnostic/therapeutic regime would not be more inhumane and illogical than the one we have now, and would certainly be more effective[18] More recently *The Times*[19] reported that in relation to problems of diminished responsibility she "sees no solution other than to allow the concept of criminal responsibility to wither away altogether "

These conclusions leave Lady Wootton once more upon common ground with a psychiatric viewpoint, and augur well for the future collaboration of the mental and social disciplines, for she would surely agree that, in the matter of social pathology, the future lies with those who study the human being and do not stop short at talking about him

RICHARD FOX
M B, M R C P, D P M

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[17] House of Lords Official Report, June 4, 1959, vol 216, no 79, col 721
[18] B B C talk, Aug, 21, 1959
[19] *Times*, Feb 13, 1960

The Widdicombe File

LXI.—*MOTHER'S UNION*

DEAR HAWKE,

I've been thinking, and I've decided that we're all wrong in our present approach to the Future of Pathology, though I'm afraid that it's almost too late to do anything about it At the moment, I reckon, most of us pathologists are suffering from a bout of schizophrenia—we desire a Proper Organisation, a Reputable Exam, a Place in the World, and a Say in our own Affairs—but this wishful thinking is without direction

Being so preoccupied with how to attain our ends, we've failed to get proper agreement first on what these ends really are—or should be The purely realistic solution would be to have a *College* of Pathology, which would have *Faculties* of Medicine, Surgery, and so on[*] After all, nobody can deny that Pathology is the Mother of Medicine, and that it embraces all the other disciplines, several of which have so regrettably developed independent colleges It would be tantamount to perversion to relegate Pathology to the hind teat of one of its children, and, if such a solution was agreed as expedient, it would give rise to complexes which would make Œdipus look simple

I am oldfashioned enough to believe in the three Rs—Reading, Writing, and Responsibility—rather than the "I'm all right Jack what can I get out of it?" approach Whatever is planned will not reach fruition in time seriously to affect my career, so I can say truly that my feelings are altruistic

If someone asked me to define the Responsibilities of Pathologists, excluding their day-to-day work, I would say they were

a *Training Pathologists*, testing them by examination and organising a career

b *Coordinating and Correlating Specialties*—because there are already too many splinter groups If we aren't careful we shall waste our substance in riotous schizogony and end up with separate journals for each organ in the body—or even their products Unless the rot is stopped now we shall eventually have journals such as *Stool*

c *Incorporating Associated Disciplines*—so that purely medical pathologists would have the benefit of the company of non-medical biochemists, physicists, &c, who are working on "medical" problems

d *Training Medical Laboratory Technicians* by establishing proper Schools of Training so that the present unsatisfactory and wasteful apprenticeship system can be abolished. It is possible by one year's full-time training to accomplish what is done in three years' apprenticeship The I M L T are doing a wonderful job in the present circumstances, but they are handicapped It is a curious fact that the worst training centres for technicians are the well-known medical schools with their laboratories split into clinical and professorial units During National Service it was found that the best-trained technicians came from the larger provincial laboratories where there is no such division of work (or loyalty)

All this means the formation of some Body with Authority, and it doesn't matter what you call this Body (Faculty, College, Institute, or Academy) provided that it can accept its responsibilities and speak with authority *directly* to the profession and to the Government without having to submit its views second hand

What I would really like to see is the family gathered together again, with each of the existing colleges contributing to the formation of a Body in which the various disciplines would meet on their one common ground—Pathology Surely the children are now mature and unselfish enough to cease worrying about making a name for themselves and being on their own? It's about time Mum celebrated her delayed diamond wedding

Yours, R M

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[*] Another pathologist, Dr Peter Davey, wrote a letter on this subject which we abstracted from the File and published on Aug 29 last Also there was a Dialogue of Today, entitled Colleges Galore, in our issue of May 9 1959 But apparently nobody ever reads anybody else —ED L.

Special Articles

GENERAL MEDICAL COUNCIL

SESSION MAY 24

AFTER SIR DAVID CAMPBELL's presidential address (reported last week) and elections to committees, the Senior Treasurer presented the finance committee's report on the accounts of the Council and the three branch councils for 1959 All four bodies finished the year with surpluses

Dr MACDONALD CRITCHLEY presented a report by the Society of Apothecaries on special examinations held in Hong Kong in October to December, 1959, with a request for the appointment of assistant examiners at further special examinations to be held there in the same period this year

The Council had before it recommendations on the training of medical practitioners in radiological health and safety that had been made by a committee established by the United Kingdom Atomic Energy Authority

The PRESIDENT, who had mentioned this subject in his address, said that he had pointed out to the committee that, while undergraduate instruction was a matter for individual schools, so far as the diploma in public health was concerned the Council was empowered to issue, not merely recommendations, but resolutions that the various teaching bodies must follow The Council, as the committee recommended in its report, would no doubt be prepared to bring the question of instruction in radiological health and safety before any special committee that might be appointed to consider changes in the curriculum for this diploma

Sir KENNETH COWAN suggested that the report before them was urgent enough to warrant the inclusion of this instruction in the curriculum for the diploma of public health as soon as possible He suggested that it might be considered whether there was anything to prevent medical schools from adding this to the curriculum for the diploma forthwith, or whether the Council should deal with the matter now, or whether a revision committee should be set up in respect of this item. Efforts were being made to cover it, so far as existing medical officers of health were concerned, by a short course, but some basic instruction should be included in the curriculum

Prof J H F BROTHERSTON said that many of those concerned with the diploma were in fact trying to do this already He suggested that the situation might be met if the Council sent a letter to the schools concerned commending this instruction to them and pointing out that it was a recommendation in the first instance He thought that the schools would take such a letter very seriously

The PRESIDENT replied that there was nothing to prevent the schools from introducing this into the curriculum He would not have thought it necessary to appoint a committee to reconsider the curriculum yet, as the present curriculum had been in existence only for five years or so If the Council agreed, however, they could write to each school, recommending and calling attention to the report. This the Council decided to do

Medical Disciplinary Committee

The committee met on May 25–27, under the chairmanship of the President

APPLICATIONS FOR RESTORATION

The Registrar was directed to restore to the Register the names of *Robert Lindsay*, *Joseph Adewunmi Ademaloyi*, and *George William Franklin*.

REMOVAL FROM REGISTER

Leslie Elgar Gardiner, registered as of 33, Wimpole Street, London, W 1, M.R.C.S. (1937), was charged with having advertised for the purpose of obtaining patients or promoting his own professional advantage (1) by writing for publication and causing to be published in 1959 a book entitled *Faces, Figures and Feelings*, (2) by sanctioning or acquiescing in the publication in the *Sunday Pictorial* of Dec. 13, 1959, of an article entitled "This Man Makes Faces" which purported to be based on an interview given by him, (3) by sanctioning or acquiescing in the publication in *Woman* of Feb 20, 1960, of an article entitled "Leslie E Gardiner, Cosmetic Plastic Surgeon", and (4) by procuring or sanctioning the publication in the issues of *Woman* of Feb 27, March 5, March 12, March 19, and March 26, 1960, of a series of articles entitled "Cosmetic Plastic Surgeon", of which he was stated to be the author—all the publications complained of including matter directing attention to his professional skill, knowledge, services, and qualifications—and that in relation to the facts so alleged he had been guilty of infamous conduct in a professional respect.

Mr S G Howard, Q.C., for the Council, referred to paragraph 5 (*b*) of the Warning Notice issued by it, under which these charges were framed He said it was a matter of considerable difficulty to determine the dividing-line between ethical and unethical He read passages from Dr Gardiner's book, and commented that anyone writing or reading it must have known that it would give the impression that the author was one of the best, if not the best, of cosmetic plastic surgeons There was no mention of any operation that was not entirely successful The jacket bore his photograph, with a biographical note and other details On the second charge, Mr Howard said that a reporter had asked Dr Gardiner questions and transposed the answers to the first person Referring to a contention that Dr Gardiner was influenced by the practice followed by other surgeons in their publications, Mr Howard said that the case must be decided on its own facts, and that, even if others had offended, this was the only case under present inquiry Newspapers tried to get articles written by well-known persons, and some liked to have medical men's names over them There was no ethical objection provided that what was written was not written so as to attract patients to the writer by drawing attention to himself

Dr Gardiner, giving evidence, said that he had been practising ear, nose, and throat surgery for twenty years, and cosmetic surgery, seriously, for nine or ten years In none of the matters mentioned in the charges had he deliberately advertised for the purpose of obtaining patients or promoting his own professional advantage He had written the book because he had found that people in this country knew little about cosmetic plastic surgery Asked about his final consent to publication of his photograph and biographical details on the dust-cover of the book, Dr Gardiner said that other doctors, of good repute in the profession, wrote books and put their picture on the back, and he took it to be the common practice. There was much evidence that other doctors of good repute, gave press interviews Cross-examined by Mr Howard, Dr Gardiner admitted having received a Warning Notice in May, 1954, *but said that he had not read it.* The purpose of his book was to finish once for all the secrecy that had existed about cosmetic surgery Questioned about his complaint to a professional organisation, he said that *Woman's Own* had contained an article which, after giving the story of an operation on a girl named Barbara, stated that the rules of etiquette prevented the magazine from giving the name of the surgeon, but they could provide a leaflet with more details of what modern plastic surgery could do for people A list of "accredited surgeons in your area" was promised Dr Gardiner then read a letter giving a list of eight names, mostly of surgeons working in Harley Street He had complained to the Medical Protection Society and the Medical Defence Union, because he was disturbed that in this " Operation Beauty " booklet it was stated to be vitally important to approach one of the accredited surgeons, and the only ones accredited were those named in the booklet At first he was told that it was a matter for the G M C , but after months they had decided to take no action whatever against the eight men

Mr F H Lawton, Q C , speaking in Dr Gardiner's defence, declared that to be unwise was not infamous conduct, nor was it relevant whether he should or should not have put himself forward to educate the public on medical matters The popularising of medical knowledge was not in itself bad and unethical Dr Gardiner had said that not a word in the *Woman* articles was by him—it was all adaptation It would be strange if there were a rule that the publication of a doctor's photograph and biography was all right on the back of a medical textbook, but that some way down the scale the photograph must be left off Was he not entitled to say it had become established practice, when distinguished members of the profession did it? He agreed that bad practice by others was no justification, but nobody had complained to the G M C in those other cases When Dr Gardiner wanted to serialise his book he had the example of an enthralling article by a famous surgeon in the *Sunday Times* and thought it accepted practice Changing times brought changing standards—there was a changed attitude, for example, to the appearance of doctors on television and the amount of publicity given to them

After deliberating in camera, the committee determined that the facts alleged under head (2) had not been proved to their satisfaction, and that therefore Dr Gardiner was not guilty of infamous conduct in a professional aspect under that charge They determined that the facts under heads (1), (3), and (4) had been proved to their satisfaction The committee deliberated further in camera, and then declared that Dr Gardiner was guilty of infamous conduct in a professional respect in relation to the facts proved against him, and the Registrar was directed to erase his name from the Register It was learnt later that notice of appeal was to be entered

CASES COMPLETED

John Cooper Gunn, registered as of 520, Littleworth Road, Cannock, Staffs, M B Glasg (1927), was charged with having advertised by the display of a notice in the sub-post office general grocery store at Rawnsley, Hednesford, Staffordshire, canvassing for the purpose of obtaining as patients three persons, and improperly transferring to his own list certain other patients The Chairman announced that the committee determined that the facts alleged against Dr Gunn had not been proved to their satisfaction and they accordingly recorded a finding of not guilty of infamous conduct in a professional respect

Patrick Francis Xavier Keelaghan, M B N U I (1942), admitted having been convicted at Prescot Magistrates' Court on Jan 19, 1960, of eight charges of unlawfully and knowingly making a false representation for a purpose connected with the National Insurance Act, 1946, when he was fined £80 Mr G K J Widgery, for the Council, said that Dr Keelaghan was in practice at Prescot and one of his National Health Service patients was a Mr Peter Marren Between June, 1958, and June, 1959, medical certificates were issued in respect of this patient which were in the usual form, stating that the patient had been examined on the date indicated on the certificate Claims for sickness benefit were made on the strength of these, and a total of £151 14*s* 5*d* was involved It was found that the patient's wife had gone to Dr Keelaghan over this period and said her husband was ill and told the doctor what she thought was the matter with him The husband gave evidence that he had been at work throughout the period, that he had not consulted the doctor, and that he knew nothing about the claims The Chairman said the committee were bound to take a grave view of the conviction, but considered that this appearance had been a warning, they had determined that the Registrar should not be directed to erase his name from the Register by reason of the conviction

Having taken into consideration the representations made on behalf of *John Maurice Leopold Burtenshaw*, registered as of Pathology Department, St. Bartholomew's Hospital, Rochester, Kent, M R C S (1931), the committee decided not to direct the Registrar to erase his name by reason of a conviction at West Kent Quarter Sessions

The committee determined that the Registrar should not be directed to erase the names of *Fintan Anthony Lennar*, M R C S (1945), registered as of Little Manor, Frittenden Green, Staplehurst, Kent, of *Gerald Green*, registered as of 6, Park Place East, Sunderland, M B Belf (1927), of *David Sproul Watt*, registered as of 416, Hyde Road, Gorton, Manchester, 18, M B Glasg (1944), or of *John Holbrook Hill*, registered as of Locks Park, Brixham, Devon, M R C S (1938) In each of these cases judgment had previously been postponed.

CASES POSTPONED

Norman Thomas Brown, registered as of 331, Bowes Road, New Southgate, London, N 11, M B St And (1923), admitted convictions in 1956 and in February of this year of being in charge of a motorcar when under the influence of drink The committee postponed judgment for a year

In the case of *Archibald Thomas Macmaster Glen*, registered as of 25, Santos Road, London, S W 18, L R C P E (1935), the committee last May postponed judgment for a year In March this year he was fined 40*s* at the South Western Magistrates' Court for being drunk and disorderly Announcing a further postponement of judgment for six months, the Chairman said that as well as asking him to furnish the names of professional colleagues and other persons of standing to whom the Council would be able to apply for confidential information as to their knowledge of his habits and conduct in the interval, they would ask him to produce evidence as to his domestic difficulties on which his solicitor had laid great stress

Serving a sentence of twelve months' imprisonment imposed at Liverpool Crown Court for driving a motorcar under the influence of drink, *Gerard Joseph McCann*, registered as of Laurel Bank, Woolton Road, Liverpool, 16, L R C P E (1949), was also charged with having been convicted of a similar offence at Liverpool City Magistrates' Court in 1954 and of being drunk and disorderly in July, 1959, when he was fined 20*s* and ordered to pay 20*s* costs Mr Widgery said that a warning letter was sent after the first offence The second was not notified at the time In the incident for which Dr McCann was sentenced to imprisonment his car knocked down a man The committee postponed judgment for two years with an appearance at the end of one

Robert Walter Simmons, registered as of Rock Villa, Salthill, Galway, M B N U I (1942), was charged with failing without reasonable cause to render all proper and necessary treatment to the late Mr Charles Humphreys, for whose treatment he was responsible under the National Health Service, failing to visit him when his condition so required or to make adequate arrangements for him to receive hospital or specialist treatment, and by his conduct neglecting his duties as a medical practitioner under the National Health Service and his personal responsibilities to a patient whom he had accepted on his list There was also a charge of having been convicted on March 28, 1960, at Cwmbran Magistrates' Court on five charges of obtaining credit by false pretences, when he was fined £50 and ordered to pay £2 8*s* costs Mr N Leigh Taylor, solicitor, of Messrs Hempons, solicitors to the Medical Defence Union, was willing for the purpose of this case to accede that there would be ground for an action for negligence against Dr Simmons, but that was a very long way from infamous conduct It did not make it any more infamous conduct that this was a National Health Service patient than if it was a private patient " It is quite clear that mere negligence cannot, in any circumstances, be infamous conduct ", said Mr Taylor If it related to one case alone it could not be infamous conduct In support he quoted a case under the Solicitors Act (in re G Mayer Cook, court of appeal, 1889), which was echoed in a recent decision under the Dentists Acts, the Felix case, decided by the Privy Council, the effect of which was to say that the Allinson case (an early General Medical Council case) was no longer of application since the passing of the Medical and Dentists Act which gave the right of appeal to the Privy Council " When you are dealing with trying to define what is professional misconduct you must have, in addition to a matter of negligence, something more ", continued Mr Taylor There had been no suggestion of any motive apart from negligence in this case The Chairman announced that the committee determined that the facts alleged against Dr Simmons had been proved to their satisfaction, and, so far as the second charge was concerned, the conviction was admitted The committee judged Dr Simmons guilty of infamous conduct in a professional respect in relation to the facts proved against him In order, however, to give him an opportunity of reconsidering his conduct they determined to postpone judgment for two years, but they would expect him to appear before them at the end of one year

Peter Louis Milbourne Hartley, registered as of 408, Wimbledon Park Road, London, S W 19, *M R.C.S* (*1941*), M B Camb (1946), was charged with having been convicted at the South Western Magistrates' Court, after pleading guilty, of ten charges of unlawfully obtaining dangerous drugs Mr Widgery said that Dr Hartley appeared before the committee in 1954 for a similar offence, when it was stated that his wife had been addicted and he obtained the drugs for her Mr Peter Baylis, solicitor, of Messrs Hempsons, said that the circumstances were very similar to those on the previous occasion Dr Hartley had never taken drugs himself The committee took a serious view of the conviction, especially in view of the earlier one, but they postponed judgment for two years

John Anthony Perpoli, M C , registered as of 11, Bank Street, Glasgow, W.2, L.R.C P E (1939), was charged with having on three occasions been convicted of driving a motorcar when under the influence of drink—in 1939, 1958, and 1959 Judgment was postponed for a year

George Horace Tancred Williams, registered as of Carramore, Barnetby-le-Wold, Lincolnshire, M.R C.S (1938), was charged with two convictions of driving a motorcar when under the influence of drink or drugs—one in 1958 and the other in 1959 Judgment was postponed for a year

James Anderson Edward, registered as of 34, Collington Crescent, Paulsgrove, Portsmouth, M.R C S (1929), had been convicted at Portsmouth Magistrates' Court in 1956 and again this January for driving a motor car when under the influence of drink. Judgment was postponed for a year

Mr Widgery informed the committee that a charge of being drunk in charge of a car was being heard against *William David Smith*, registered as of 118, Marlborough Park Central, Belfast, M B Belf (1959), the following week. Dr Smith appeared for postponed judgment, and judgment was again postponed

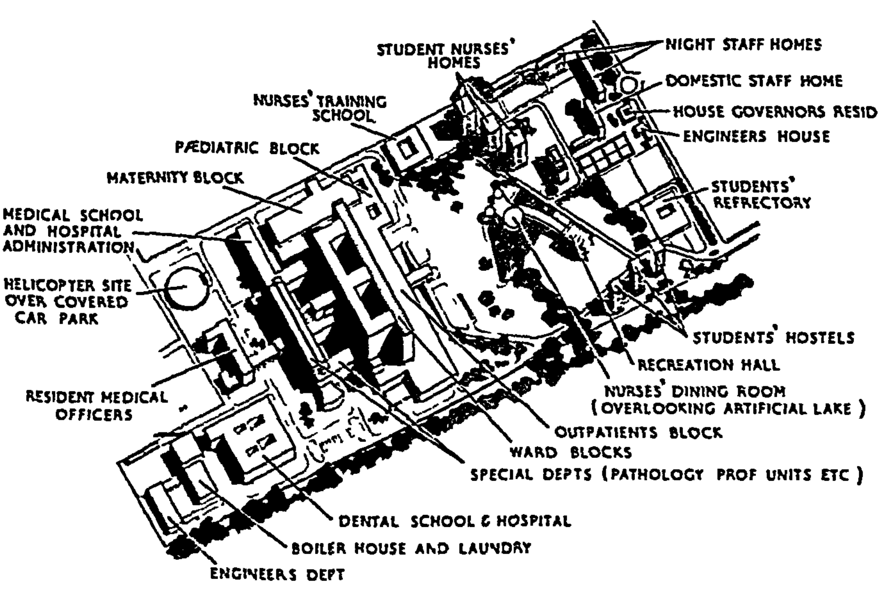
UNIVERSITY HOSPITAL OF WALES

THE architectural competition for the new medical teaching centre which is to be built on a 53-acre site at Cardiff has been won by Messrs S W Milburn and Partners in association with Mr M Harding, A R I.B.A , and Mr J Surtees, A R I B A

For the first time in this country accommodation for the treatment of patients and for the teaching of students is being planned and built as a whole from the beginning, and the largest building on the site is the combined hospital and medical school which occupies about a quarter of the site The ten-storey hospital will have 650 beds in the main ward block, which faces south-east It is linked with the four-storey medical school and the residents' quarters Behind it stands the dental school and hospital

The compact design of the main building has allowed the architects to group the other buildings in a parklike setting A small stream which flows through the site is to be dammed to form a small lake The nurses' dining-room will be built over part of this and a flyover bridge will lead to their hostels Another example of enterprising planning is the helicopter landing site which has been made on the roof of the covered car park

The centre is to cost about £7 million to build and furniture and equipment another million Owing to the acute shortage of dentists, especially in Wales, the dental school and hospital is to be part of the first stage to be built It is hoped that the first yearly entry of 50 dental students will begin their clinical training in *1964* The medical school will have a yearly entry of 65 students



The assessors of the competition were Sir Percy Thomas, P P R I.B.A (chairman), Mr F R S Yorke, F R I.B.A , Mr J H Forshaw, F R I B.A , Provost A Trevor Jones, F R C.P , and Dr A R Culley The second prize was awarded to Mr Charles E Pearson, F.R I B.A , Charles B Pearson & Son, of Lancaster, and the third prize to Messrs Farms and Partners, *of London* *There were forty* entries to the competition

The designs submitted, including those of the three prizewinners, will be on public display at the Ministry of Health, Savile Row, London, W 1, from July 7 to 14

In England Now

A Running Commentary by Peripatetic Correspondents

THERE is much to be said for publication as a spiritual discipline To begin with, of course, there is the little matter of doing the work so as to have something to publish, but it would be a mistake to overemphasise this side of the affair, since with the triumphant march of modern medicine it is apparently becoming superfluous The real struggle between the dignity of Man (i e, you) and the ineluctable forces of an impersonal hostile universe (i e, the Editor) begins only when the first fair sheet of paper is ravished by your pen

Temptations are many The most insidious of these is the desire to preface your observations on the courtship behaviour of Siamese fighting-fish in a 2% solution of tranquilliser with some kind of all-embracing statement on the nature of scientific knowledge or the meaning of the principle of verifiability The most human is the impulse to take a stab at a theory propounded by the man who got the job you wanted The most abominable is the combination of exhibitionism and obsessionalism which leads you to head your paper with an irrelevant quotation, out of context, from St Augustine or Edna St Vincent Millay, and then to refer to every paper with a title which contains one or more words in common with yours

Having avoided most of these pitfalls, you rewrite the text two or three times until it says exactly what you want You send it to the journal you had in mind It is three times too long You can cut it down to half, and the bones of your emaciated piece stand out with embarrassing sharpness and clarity All those paragraphs of discussion in which you forestall the attacks of a hypothetical critic who seems to know all your secret doubts and reservations have had to go In place of your original unassuming detachment there have appeared, in successive drafts, a detectable inclination in favour of hypothesis A, an obvious bias towards hypothesis B, and finally a proud declaration of faith in A

At last, the proofs arrive and are returned But now comes the second stage of labour Long weeks go by, you lose confidence in your work, you lose the sustaining image of an international audience athirst to read your contribution to Britain's reputation It is a trying time and one is never far from despair Suddenly, one day, a friend approaches you with a subtle half-smile "Hello," he says, "I read your letter in *Misbehaviour* the other day I really liked it—most amusing" You have arrived, but you realise that travelling hopefully wasn't so bad compared with this The last stage in the humiliation comes when an astronomer or a plastics chemist—someone from a totally irrelevant and tiresome discipline—writes to say that he found your letter to *Misbehaviour* quite absorbing, but did you know that Spishnik and his team at Staroi-Chelavek had hit on the same thing in 1923?

* * *

"Well, I don't like to complain, doctor, but couldn't it have been a bit more private? There was me, lying there as God made me, with the specialist and nurses around, and who should come in but that girl of Mrs Brown's from over the road, she works there I suppose, with a stack of papers and that silly smile on her face 'Why, hallo, Mrs Hatfield!' she said"

* * *

I see that a medical M P recently protested that the police had towed away his Bentley in the Harley-street area while he was seeing a patient He seemed amazed that they had the temerity to lay hands on it since it bore House of Commons and B M A badges Big game, obviously, and just the sort of catch to appeal to some zealous traffic cop

Smaller fry are sometimes thrown back to fatten At least, I can think of no other reason for the more lenient treatment of my Morris Minor (My wife had taken the Bentley and I was too lazy to get out my bike) It was early one morning and I had parked rather on the corner near my consulting-room, also in the Harley-street area Wearing grey flannels and a sports jacket, I meant to nip in for my letters but was delayed a few minutes by my receptionist On returning to the corner my car was gone Not for a moment did I flatter myself that it had been stolen, so I plodded along to the nearest blue-lamp H Q Yes, said a burly sergeant, consulting a ledger, they had towed my car away to Paddington Green A lorry had had to reverse to get round that corner, therefore I was causing an obstruction I apologised humbly, managed to convince him that I was a doctor despite my casual garb, and brandished the four circulars advertising tranquillisers, two bills, and a picture postcard from a friend on holiday in Venice as proof that I had been to collect my letters The sergeant conferred with a colleague and came back smiling One of the constables was going over to Paddington Green and if I cared for a lift in a police car strictly off the record, of course So I was driven in a black police car by a smart young policeman He kept his eyes sternly on the traffic, gave all the correct signals, and halted punctiliously at the zebra crossings, while he expatiated on the improvement in the flow of traffic since the new parking meters had been introduced in the West End Even so, he complained, some motorists persisted in parking in the most dangerous manner I nearly joined in with some self-righteous condemnations, but on the whole I thought it more tactful to remain silent

* * *

Like my fellow peripatetic, I too as a student learned Occam's splendid tag Alas, the hallowed Razor has itself been multiplied beyond necessity (save that, perhaps, of Man's eternal need for myth) For that phrase by which we common folk remember Occam—is myth It first saw light in 1639, when it belonged to John Ponce of Cork, "A man of great abilities and independent disposition" As for William, it was first attributed to him much too late for any good it could do him—in 1812, to be precise And as for us, its use is "a serious philosophic corruption"[1] Good Occam, we shall miss his neat phrase when scholarly precision finally deprives us of our myth

* * *

Last year I was on holiday with a group of people who were all very keen photographers While I wandered around with my box camera slung around my neck as if I'd put it there by mistake, they fixed close-up lenses to their Leicas and took portraits of spiders, or planned artistic colour films of the sunset. When they weren't using their cameras they were talking about them The subject seemed to me ineffably boring, and I vowed never to take up photography

Summer passed, winter ended, spring approached I considered the matter, and decided that my camera, faithful friend, was due for retirement Not, of course, that I cared about photography, but it is pleasant to have a record of one's travels, I would buy another camera I studied the choice available, and made up my mind to buy a simple roll-film one My studies involved some consideration of *f* values and shutter-speeds, it seemed necessary to find out about them so as to make the best use of my money Eventually I made my final choice. I wanted nothing complicated, and certainly not a miniature camera

Pay day came, and I set out one Saturday to buy my camera I reached the shop and went in As if in a dream, I heard myself saying, "I'm thinking of buying a miniature camera"

Half an hour later I emerged with my camera, and without a good deal more money than I had intended to pay I must go back there soon though, as I need an exposure meter, lens hood, filters, tripod, and if possible a rangefinder I wonder if three shutter speeds are really enough?

* * *

Overheard at the Medical Disciplinary Committee—*Q*—Had the doctor received the letter from hospital?—*A*—No You see I was only three weeks since I left hospital

* * *

STATISTICAL PLOY

A malignant old Proband from Bude
Told a Cohort "*I'm going to be rude*
It's a pretty fair bet
Your survivals are nett,
Whereas *mine* is emphatically crude"

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[1] Thorburn, W M, *Mind*, 1918, 27, 345

Letters to the Editor

PROGNOSIS FOR ALCOHOLICS

SIR,—Alcoholics comprise many different personalities, and the predominance or otherwise of certain personality types (e g , of psychopaths) in a given group of cases makes it almost impossible to compare the results obtained by different observers with different methods [1 2] However, the results and the prognostic pointers reported by C G Berglin on the basis of disulfiram therapy in Swedish alcoholics (May 7, p 1033) bear a very close resemblance to findings in English alcoholics treated by a more comprehensive psychological-physical approach,[2 3] which often incorporated disulfiram ('Antabus ') [4]

Thus, older, married alcoholics had in general a better prognosis than the young, unmarried, or divorced ones Indifference to their alcoholic problem, criminal and poor work record, and methylated-spirit drinking [5] were by and large also pointers to a poorer prognosis Among the Swedish as well as among the English alcoholics it was the abuse of alcohol at a young age which was of prognostic significance but not (as reported in your review of Berglin's findings) the mere " history of drink before the age of 21 "

In a carefully planned investigation of American hospitalised alcoholics, comparing the results of four different treatment methods, Wallerstein et al [6] found disulfiram " the most helpful to the most patients " Yet the number of patients in whom disulfiram failed, and that of those helped by other therapeutic methods, was large enough " to preclude the blanket prescription of Disulfiram as the optimal hospital treatment of the chronic alcoholic patient "

In view of these findings and having regard to the different types of personalities among alcoholics, a more comprehensive therapeutic approach based on the evaluation of the needs of the individual patient seems in theory preferable to the method of relying on one and the same approach in each patient Berglin's results are therefore all the more remarkable But perhaps more important is that this Swedish study indicates once more that, provided the problem is tackled systematically and constructively, the prognosis in alcoholics is much more hopeful than generally assumed by the medical and the lay public

St Bernard s Hospital, Southall,
Middlesex. M M GLATT

PERTHES' DISEASE

SIR,—I have taken the opportunity of a visit to Rio de Janeiro to inquire about the local incidence of Perthes' disease among Negro children admitted to the hospitals of the Brazilian ex-capital

I am obliged to Prof Dagmar Chaves for the figures of Perthes' in the Hospital Escola Anchieta, which fills about half of its beds with Negro children Of the 55 patients diagnosed both clinically and radiologically as Perthes' disease, 54 were white and 1 was a mulatto Dr Oswaldo P Campos kindly gave me the figures collected in the Hospital Jesus, also in Rio de Janeiro, more than half the admissions to this hospital are Negro children From 1935 up to the present time they have treated 232 cases of Perthes' disease of these, only 9 were Negro

These figures show that if the condition is not unknown even among Brazilian children of African origin, its occurrence is rare Adding up the cases which have been seen at both Brazilian hospitals, only just over 3% are of African stock

In my initial letter of Jan 13, my reference to the alleged rarity of Perthes' among children of African origin was mentioned to suggest an anatomical explanation, perhaps now only valid for some of the Negro population—namely, that the blood-flow to the upper femoral epiphysis may be secured in those groups of population resistant to Perthes' by the presence through childhood of the vessels entering the epiphysis through the ligamentum teres, a factor which does not occur in the white child

It may be of interest to note that in 6 well-injected specimens of femoral heads from African (Bantu) children and 1 Brazilian which I have been able to examine, under the age of 4, all but 1 African had the round-ligament vessels permeable to the injected mass deep into the epiphysis I am grateful to Dr S Schulman of Johannesburg and Dr Nova-Monteiro of Rio for their collaboration

I must state my appreciation to Dr Cockshott and Dr Palmer and to Mr Golding for their constructive contributions, and to Prof W W Davey of University College Hospital, Ibadan, for arranging a fuller investigation of the blood-supply of the femoral head in Africans during growth

Nuffield Orthopædic Centre,
Oxford J TRUETA

MEDICAL ASPECTS OF ROAD SAFETY

SIR,—The second of Dr Norman's extremely interesting Milroy lectures (May 7 and 14) reminds me of a further type of disability which poses similar problems On several occasions during recent years I have been asked to report on the fitness to drive of men of low intelligence, and in some instances the decision is indeed a difficult one

As a general rule those certified under the Mental Deficiency Acts are not allowed to hold a licence, though it is known that some engaged on farm work have driven a tractor in the field After their discharge from Order they may feel entitled to answer " No " to question 15 of the application form which reads " Are you suffering from any disease, mental or physical ", and within my experience several have become drivers

Others have never been certified under the Acts, but have been on statutory or voluntary supervision Again, while under supervision, they have difficulty in obtaining a licence, and the assessment of their fitness for discharge so that they can obtain one calls for careful consideration of many factors

Ability to drive cannot be equated with degree of intelligence, and most of us know of men of superior intellect who, because of inattention or introversion, are not the most capable drivers If my memory serves me aright, men of selection grade IV were regarded as suitable for driving in the Army Thus it is difficult to fix an intelligence-quotient limit beneath which a man should not hold a licence, though certain generalisations are permissible

By and large, those with an I Q of 70 or over have the potential to become good drivers, though if illiterate they need special tuition to recognise road signs The holocaust on the roads is so great that those with an I Q of below 50 should not be given a licence Even if they are physically fit, their comprehension is so limited, and their cerebration so slow, that they are likely to prove a menace on the roads

It is with those between these limits that the chief difficulty arises Some may lose their employment as farm labourers unless allowed to drive a tractor, and, if they are emotionally and temperamentally stable, some are capable of handling such a slow-moving vehicle competently and should be allowed to do so Whether such a person should be permitted to drive a car or motor-cycle calls for judgment based on long experience, and each must be judged as an individual on his performance and aptitude

Undue apprehension that such men should be driving on the road may be allayed if I mention that I have on occasion noted one of my ex-patients controlling a road block with his red and green flags, and that he waved on the lines of traffic as ably as any other roadman

The Royal Hospital,
Starcross, Devon D PRENTICE.

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1 Williams, L *Lancet* 1952 i, 787
2 Glatt, M M *Brit J Addict* 1955, 52, 55
3 Glatt, M M *Lancet*, 1959, ii, 397
4 Glatt, M M *J ment Sci* 1959 105, 476
5 Glatt, M M *Lancet*, 1956 i, 752
6 Wallerstein, R S , Chotlos, J W Friend, M B , Hammersley, D W., Perlswig, E A , Winship, G M Hospital Treatment of Alcoholism, p 176 London, 1957

EXPIRED-AIR RESUSCITATION

SIR,—The paper by Surgeon Lieutenant-Commander Cox and his colleagues and your editorial of April 2 rightly stress the superiority of expired-air resuscitation over manual methods. The interesting problem is why the older inefficient methods gave such good results, for the mortality from drowning when assistance is at hand (we cannot hope for much in other circumstances) seems to have been extremely small. Spontaneous respiration apparently began in most, though not all, surviving cases within two minutes or so, an inadequate period of time with, for example, the Schafer method, to improve significantly arterial oxygen or carbon-dioxide levels. If, then, recovery in these cases is not due to anoxia, and if our therapeutic zeal (rightly) precludes our assuming that it is spontaneous, what is it due to?

Perhaps the success of the older methods lies merely in the rapid application of a mechanical stimulus. The anæsthetists of yesteryear pulled rhythmically on the tongue and even today the new baby's bottom is frequently smacked, both techniques are attended, I understand, by a measure of success. There would be little point in putting forward a hypothesis which it is difficult to prove were it not for the risk that the current emphasis on a perfect airway and ideal alveolar ventilation—an emphasis doubtless attributable to the anæsthetic experience of those who have pioneered later methods—may lead to delay. It may well be that any inefficient method applied immediately may be preferable to an excellent one applied a minute or two later. In the present inadequate state of knowledge concerning the mechanism of recovery in these patients the need for speed must be constantly and forcibly reiterated.[1]

For this reason alone, the dismissal of the direct methods (mouth-to-mouth and mouth-to-nose) by your contributors must not be readily accepted. While equipment may be a help to the professional rescuer no method involving apparatus can be recommended to the general public, if only because mother will not have time to get to the bathroom cupboard and back when Johnny falls in the fishpond. As with many procedures distinctly more revolting, the æsthetic objections are more awful in contemplation than in the event: they are likely to be forgotten in the heat of the moment, particularly if they are taken for granted by teachers and not publicised as valid objections.

Incidentally, I should be most grateful if any of your readers could quote accurate statistics for the mortality of drowning when assistance was nearby.

East Melbourne,
Victoria

BRYAN GANDEVIA

SIR,—The letter from Dr. Buxton (May 21) brings to mind the well-known dictum "error supports custom, custom countenances error" (Milton).

In the type of patient with emphysema and decreased lung compliance which he mentions, ventilation is difficult at best. The most effective way to ventilate such a patient when he becomes apnœic is to use a method that will cause a great enough pressure gradient in the airway to support adequate ventilation. Perhaps Dr. Buxton has noted this in the article[2] referred to, but I could not find his paper in our library. In any case, the above requirement can best be provided by direct artificial respiration—as any respiratory physiologist, or any physician who has studied this problem, knows very well. Why, then, should Dr. Buxton continue to support the medical advisers of the St. John Ambulance Association and the British Red Cross Society, who feel that the Holger-Neilsen method is the best to resuscitate such a victim?

Considering all aspects of this controversy, I feel that the medical advisers of lay bodies who supervise training in artificial respiration should look at all the evidence fairly—the negative as well as the positive. My own detailed studies of this subject have convinced me of the wider efficacy of the direct methods of resuscitation over any known manual methods.

University of Saskatchewan,
University Hospital, Saskatoon

ALLEN B. DOBKIN

THE PREVENTION OF TETANUS

SIR,—Tetanus immunisation, to be successful, requires the administration quinquennially of reinforcing injections and the immediate availability of the patient's immunity history at a time of injury. Your support (May 21) of the tattoo mark for record purposes could with advantage have been amplified by some indications of how it would be applied nationally. To be worth while, the tattoo marks would have to be standardised and to indicate when the immunity state had been achieved. An additional mark giving similar information would need to be added for each reinforcing injection, and each of the many general practitioners now happily giving triple antigen to his patients would have to add tattooing to his other accomplishments.

Apart from the æsthetic objections that would lead very large numbers to refuse tattooing, the possibility of establishing a successful national tattoo register seems to me even more remote than the development of a combined disc and card system.

Health Department,
Municipal Building,
Preston

J. S. G. BURNETT
Medical Officer of Health.

S's

SIR,—I am constrained to rebuke you for a grammatical horror usually committed (and I believe conceived and born out of grammatical wedlock) on the other side of the Atlantic. I refer to your method (? increasing) of forming the possessive case of proper names ending with the letter *s*.

Two examples will suffice, from your issue of May 14. Professor Morris's name is Morris, *not* Morri, which is the only way one can pronounce Morris'. Sir Hans Krebs's name is Krebs, *not* Kreb, which is similarly the only manner in which one can pronounce Krebs'. The genitive forms of such surnames cannot decently be formed in this way, and to attempt to do so is a grammatical gaffe that offends the eye and the ear, and creates a mental fence one's mind has to pause and leap before it gets on with the subject matter.

Do you expect your readers to read the names as Morri and Kreb, or to supply mentally the *s*'s that would correct your blunder? If you do not, is not your editorial eye affronted by the bizarre, not to say, clumsy, appearance of this unpleasant form?

West Folkestone,
Kent

B. G. EDELSTON

⁂ "It was formerly customary", says Fowler, "when a word ended in -s, to write its possessive with an apostrophe but no additional s, e.g., Mars' hill, Venus' Bath, Achilles' thews." Some years ago we reverted to this pleasantly literary practice because we were tired of the utilitarian Graves's and Moses's which nobody pronounces as such. But, even in 1926, Fowler thought that s' should be reserved for "poetic or reverential contexts". Our revulsion may have been needlessly complete, and the time may have come for a compromise—perhaps based on how the words sound. In the internecine strife still continuing between St. Thomas's Hospital Medical School and St. Thomas' Hospital the school will, we think, emerge as victor—especially now that London Transport has firmly changed its station from St. James' to St. James's Park. If, recognising these hard facts, we follow Fowler, we shall at any rate avoid Moses's and Achilles's, because they are reverential, and we could get round Graves's by using the name as an adjective, writing Graves disease just as we already write Krebs cycle or Coombs test Certainly Perthes disease may be an improvement on either Perthes' or Perthes's But if pronunciation is to be the guide, the possessive form will still be needed for names not ending in s Nobody talks of Parkinson disease or Pott fracture.—Ed L.

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[1] Donald, K. W. *Brit. med. J.* 1955, ii, 155.
[2] *Med. Pr.* 1956, 236, 611.

"PSYCHOLOGICAL OVERLAY"

Sir,—Miss Kay (May 21) does well to expose the hateful tendency both in hospital and general practice to insult the patient with such obscurantist nonsense as "psychological overlay" instead of frankly admitting one's own inadequacy The word "neurosis" should be erased from the medical dictionary!

London, S.E.13 Allan Chatelier.

ADDICTION TO DRUGS

Sir,—In commenting on my letter of March 7, Dr Stungo (May 21) quotes me as "inaccurate" in saying that there was no narcotic problem in the United Kingdom because there narcotics are freely dispensed by doctors to all askers I did not advance that as an accurate statement of fact I merely meant to convey, accurately, that such reports are frequently seen in the press in America and it was intended as an example of misinformation extant respecting the narcotic situation in our two countries

Additional misconceptions might arise from Dr Stungo's letter He implies that there are no legal criminal sanctions against the abuse of narcotic drugs in the U K when there is no medical indication The fact is, of course, that there is a substantial body of English law not too different in intent from that of the U S.A

There is also the mistaken implication in Dr Stungo's letter that treatment is not available to addicts in the U S.A "without charge and without penalties" Of course, treatment is available, extensively, including two Federal narcotic hospitals which probably represent the world's most elaborate ventures in this field There is a difference in emphasis in the two countries, as might be expected because of differences in the problem. Among the few English addicts there is a high percentage of persons of such background and culture as will respond to measures of a non-coercive type—or where the compulsion is latent Such measures would not in any respect be effective with most of the hedonistic underworld characters making up the bulk of the large city concentrations of American addicts On the other hand, California medical authorities report that of the relatively few physicians who become addicted in that State, about 92% are rehabilitated and most quite promptly Temporary loss of the right to dispense or prescribe narcotics, and sometimes temporary suspension of the right to practise medicine, are usually enough to accomplish this end

In Hong Kong there exists a drug traffic far greater in extent and intensity than anything ever seen in America, even at the high point of addiction which existed before we embarked on our present law enforcement programme and international control Recently, in a white-paper, the Hong Kong Government recommended, among other things, more law enforcement against narcotic traffickers, with more severe penalties A programme-operating emphasis which might suffice very well for the law-abiding United Kingdom population which does not "go' for opiates as a dissipation (*and never has*) might be most unrealistic in America and for Hong Kong

According to United Nations document E CN 7 355, dated Feb 10, 1960, the consumption per 1000 inhabitants in 1958 was

	United States	*United Kingdom*
Morphine	436 doses	1211 doses
Heroin	None	185 doses

Dr Stungo is inaccurate in ascribing the spread of U S narcotic addiction to the profits from the illicit traffic Analysis of thousands of specific cases of addiction establishes beyond argument that the inception of addiction in a great proportion of cases has little relation to the profit motive of the peddler The vice is here spread by means of social contacts, the attraction is the opiate. Forty-five years ago, when narcotic drugs could be freely bought over the counter—without profit to any "criminal vested interests" let us note—we had 1 addict in about every 400 of the population. Today, this count is down to close to 1 addict in 4000 The daily intake of poison per addict in those early days was 5 to 10 times what it is now The addict doesn't care where his stuff comes from The cheaper and the more readily available the greater the intake

People who do not understand the sinister characteristic of opium use to spread in a receptive environment might ponder on the "Opium Wars" of about a century and a quarter ago When intrepid American and British shipmasters dumped opium on the Chinese beaches at gun point, they did not find it necessary also to send "detail men" inland to seduce the population That circumstance needed no further outside help

Washington, D C M L Harney

HISTORY AND THE PARASTERNAL LYMPH-GLANDS

Sir,—I was interested in Mr Richard Handley's comment in your issue of March 26 on "the first known record of interest in the spread to the internal mammary lymph-glands of cancer from the breast" As he pointed out, Halsted's remarks in 1898 were not the first known record, for as far back as 1790 this metastasis had been noted by Cruikshank.

Cruikshank was a protege of John Hunter It is therefore of interest that Hunter[1] himself was also aware of metastatic invasion of the internal mammary lymph-nodes in breast cancer Thus, in his lectures during the years 1786 and 1787, "taken in short-hand by Mr Nathaniel Rumsey of Chesham" and published by Dr J F Palmer in 1835, we find that Hunter, after dilating upon the spread of the tumour to the axillary and supraclavicular nodes, added that "the contamination extends in other instances on the inside of the sternum, in the course of the internal mammary artery"

Lymph-borne metastasis is characteristically centrifugal It is of interest, therefore, that in the 1825 edition of the lectures of Sir Astley Cooper,[2] it is noted that "the glands behind the cartilage of the ribs, when the disease is placed upon the sternal side of the nipple, are generally diseased"

Another interesting feature of lymph-node metastasis is the "skipping" of some well-known lymph-node groups on occasion In this connection, as far back as 1819, Samuel Cooper[3] did remark that breast cancer may at times affect only the lymph-nodes "towards the sternum" Or, as Gibson[4] put it in 1832, "sometimes the glands of the axilla are not affected, while those near the sternum or in the intercostal spaces are thoroughly contaminated"

On the whole, therefore statements concerning the priority of certain publications are apt to be controversial This has been the bane of eponyms Three centuries ago, William Harvey[5] was involved in a priority claim and he summed up the problem nicely in a letter dated April 28 1652 'Why

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1 The Works of John Hunter (ed J F Palmer), vol 1 pp 201 628 London 1835
2 The Lectures of Sir Astley Cooper (ed F Tyrrell), vol 2 p 183 London, 1825
3 The First Lines of the Practice of Surgery (by S Cooper) vol 1, p 262. London, 1819
4 The Institutes and Practice of Surgery (by W Gibson), vol 1, p 220 London, 1832
5 The Works of William Harvey (translated by R Willis), p 552 London, 1847

may not the thoughts, opinions, and manners now prevalent, many years hence return again, after an intermediate period of neglect?"

Pathology Department,
Western Infirmary,
Glasgow

W I B Onuigbo

THROMBOPHLEBITIS FOLLOWING INTRAVENOUS INFUSION

Sir,—Your interesting leading article of April 23 omits one ætiological factor which, though perhaps taken for granted by many, bears re-emphasising I refer to poor aseptic technique resulting in infection of perivenous and venous tissues

Too many of us are occasionally guilty of inserting an infusion needle after no more than a cursory wipe of the patient's skin with a swab moistened with spirit Unfortunately examples of such carelessness are not confined only to percutaneous ("push-in") infusions, but have been observed even during venous dissection ("cut-down") for infusion Under such disadvantageous conditions it is no wonder that infection results

Operation-site skin is always meticulously prepared, and although the preparation of infusion sites in similar fashion would be regarded as absurd, let our approach nevertheless be realistic Surely very little more attention to aseptic detail could not be anything but a step towards diminishing still further the incidence of thrombophlebitis in those unfortunate patients who must endure intravenous infusions for long periods

Durban,
South Africa

P H B Maytom

RAISED INTRACRANIAL PRESSURE ASSOCIATED WITH TRIAMCINOLONE

Sir,—We were interested in the letter from Dr Laurance and his associates (March 26) describing two children with severe asthma who developed raised intracranial pressure whilst on treatment with triamcinolone They quoted Valentine,[1] who suggested that triamcinolone had produced intracranial hypertension in a child with nephrosis We have recently seen two children with chronic eczema who developed the syndrome of benign intracranial hypertension whilst on treatment with steroids but who had not received triamcinolone

Case 1 —An eight-year-old boy was admitted under Dr P R Evans, in February, 1960, with one week's history of headache, vomiting, and drowsiness He had been treated for eczema since three months of age and had received prednisolone orally 5–10 mg daily for the past twelve months He had bilateral papillœdema but no other neurological signs Ventriculography revealed a normal ventricular system Symptoms ceased within a week and his papillœdema had almost completely disappeared one month later, although prednisolone therapy was continued

Case 2 —A five-year-old boy with chronic eczema had been treated with non-greasy hydrocortisone alcohol ointment for sixteen months He was admitted under Dr C T Potter in March, 1960, with one week's history of headache and vomiting The only abnormality in his nervous system was bilateral papillœdema Lumbar encephalography showed normal cerebral ventricles He improved soon after admission and the papillœdema had disappeared one month later

Case 2 is of special interest because he seems to be the first reported case in whom this complication has occurred during treatment with topical steroids, suggesting that hydrocortisone may have exerted a systemic effect after absorption through the eczematous skin [2,3]

We should also like to draw attention to the article by Dees et al [4] describing three boys with asthma who developed benign intracranial hypertension during treatment with steroids They had been treated with oral cortisone, hydrocortisone, prednisone, prednisolone, methylprednisolone, and occasional injections of corticotrophin, but only one boy (case 2) had received triamcinolone It appears, therefore, that intracranial hypertension may complicate therapy with a number of steroids besides triamcinolone

A detailed account of these cases will be reported elsewhere

Guy's Hospital and
Evelina Children's Hospital
of Guy's Hospital,
London, S E 1

P F Benson
P O D Pharoah

HEPATITIS AFTER INOCULATIONS

Sir,—It is unfortunate that in your leader of March 5 you felt it necessary to bolster up your case with such unfortunate arguments

In the Middle East epidemic of 1942–43 the incidence of jaundice was certainly more among officers than other ranks but this was definitely not due to their excess of inoculations. The incidence of jaundice was greatest in officers and common in other ranks of the British forces, very high in all ranks of the New Zealand Division, common in officers (mainly British) of the Indian Division, and almost non-existent in Indian other ranks A far better explanation, and one I have always taught, is that the infection was probably carried by poorly washed eating utensils These might easily be shared by officers messing together, would be less likely to be mixed among troops using mess tins, and might well be mixed more among the New Zealanders of all ranks with their attitude of complete equality and lack of any caste system among ranks The Indian troops on the other hand, with the strict caste system and habit of consuming their food with the left hand and never using eating irons, would be exposed to little or no risk of infection

Jaundice was a hazard of war long before inoculations were thought of, and incidentally in this particular epidemic it was found when we advanced that the enemy forces were suffering similarly

Your example (the consultant, who with his wife and three children, received a polio injection and two of the five developed jaundice five months later) of possible spread by injection seemed to me equally far-fetched Surely two cases of the same infection disease in the same family in the same environment is so common that such an abnormal cause need not be postulated

That individual needles for injection is desirable cannot be questioned even if it is difficult for emergency mass inoculations, under primitive conditions, and I can never understand why the portable 'Surqualet', or other electric steriliser, has not been more widely used, for this small and inexpensive instrument is ideal both for clinic and private practice

Ngwhatu Hospital, Nelson,
New Zealand

R L Haviland Minchin

⁂ The particular arguments criticised by Dr Minchin are certainly not the strongest part of the case in favour of our proposition that a separate sterile syringe and needle are required for each inoculation Since the causal agent of hepatitis has not been cultured there is inevitably more than usual difficulty in making a final assessment of all the available evidence—some parts of it are much stronger than others

We are glad to note that Dr Minchin does not dissent from the practice we recommend Electric boiling-water sterilisers (which we presume the 'Surqualet' is) have two main disadvantages for mass inoculations (1) a large team of careful and conscientious helpers is required to keep a steady flow of sterilised, cooled, dried, reassembled, and charged syringes in the hands of the inoculators, (2) the pressure of time on the helpers usually leads to dangerous short-cuts with serious reductions in the boiling time and faults in the methods of assembly

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[1] Valentine, G H Lancet, 1959, i, 892
[2] Malkinson, F D J invest Derm 1958, 31 19
[3] Stoughton, R B J Amer med Ass 1959, 170, 1311

[4] Dees, S C, McKay, W, Jr Pediatrics, 1959, 23, 1143

In our view, for mass inoculations in difficult conditions, ready sterile dry syringes will prove to be particularly useful and may indeed be the only practicable method of guaranteeing a separate sterile syringe and needle for each inoculation —Ed L

CHROMOSOME CONSTITUTION OF MONGOLS WITH LEUKAEMIA

Sir,—The occurrence of an abnormal chromosome constitution in mongols may have significance other than simply in relation to the ætiology of mongolism[1–4] The possible role of the extra chromosome material in determining the increased risk of mortality from leukæmia which has been found in mongols[5–7] may well be relevant to the general problem of leukæmogenesis Such relevance seems the more likely in view of the demonstration of chromosome abnormalities in some cases of acute leukæmia[8, 9] We have been trying for over a year to study the chromosome constitution of mongols with leukæmia Such cases are, of course, fairly rare, but during this period we have had the opportunity of studying two such patients However, during the same period we heard of a further four cases only after death, and the clinicians concerned expressed regret that they did not know of our interest

It is for this reason that we seek wider publicity for our wish to study mongols with leukæmia. Although the blood and bone-marrow samples for chromosome studies require special handling immediately they are obtained, it must be emphasised that such samples can be taken at the same time and in the same way as those required for ordinary diagnostic purposes We should be grateful for the opportunity to study these patients anywhere in Britain

Medical Research Council Group for
Research on the General Effects
of Radiation,
Department of Radiotherapy,
Western General Hospital,
Crewe Road, Edinburgh, 4

A G Baikie
W M Court Brown
P A Jacobs

NAMES OF DRUGS

Sir,—Surely it is time for some action on the names of drugs Dr Philip[10] suggested that a suitable registration number for a drug could convey the more important data concerning it Your review[11] of *A Pocket Book of Proprietary Drugs* said " It will be very useful in identifying the constituents of strange-sounding preparations "

It would be a start if all drugs had identifying letters showing their use—e.g, penicillin AB (for antibiotic) iodine AS (for antiseptic)

The task of simplifying and reducing the number of names of drugs might be undertaken by the Joint Formulary Committee

Beck Laboratory,
Swansea Hospital

H C M Walton

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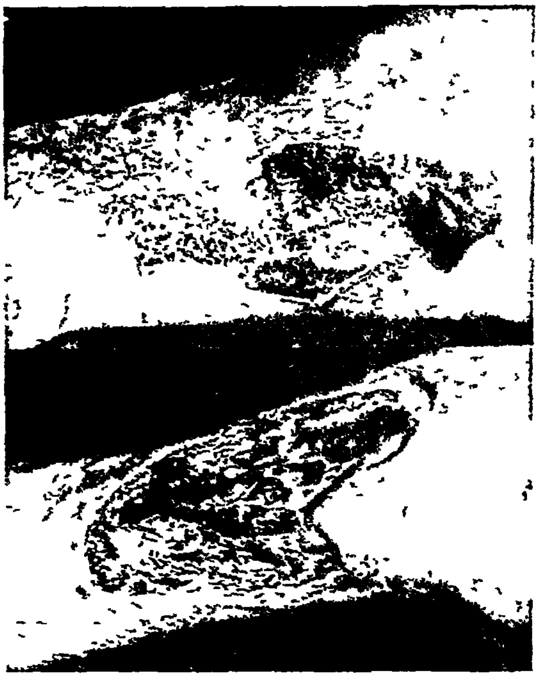
REDUCTION OF INTRACRANIAL PRESSURE WITH HYPERTONIC UREA

Sir,—The experience of Dr John Stubbs and Mr Joe Pennybacker (May 21) with hypertonic urea is most interesting and helpful I wish to support their claim of its value. Indeed the reduction of intracranial pressure and improvement in handling characteristics of the brain make the use of hypertonic urea and invert sucrose one of the real technical advances in intracranial surgery

The absence of local tissue necrosis at the point of infusion speaks well for their technique of administration.

Extravenous leakage is a very serious accident, and in one of my cases was followed by severe tissue necrosis Probably a large amount of the solution escaped into the subcutaneous tissue, for this is the only case in which diuresis and reduction of intracranial pressure did not occur—a fact continually remarked on during the operation Necrosis declared itself within 4 hours, and continued for 4 or 5 days



Above One day after operation Commencing necrosis
Below One month after operation. Resulting ulcer

Administration should, I think, be by an intravenous catheter and away from important nerve and artery concentrations The necrosis seems to be caused not by the urea but by the products of its breakdown Leakage of the solution should therefore be treated by incision of the area, washing out the wound with saline, and leaving it open for secondary suture

Dr Stubbs and Mr Pennybacker do not say what they think about the use of hypertonic urea with hypotension, nor (though basal aneurysms are specified among their operations) whether they have had experience of its use when renal filtration pressure is abolished I have avoided the use of hypotension and hypertonic urea, but their views on this would be valuable because diuresis is apparently not the only factor affecting the handling characteristics of the brain

I hope that the indiscriminate use of hypertonic urea in head injuries may be avoided Nothing could be worse for a patient with an extradural hæmatoma developing than to have a dose of this very powerful medicine As with almost everything else in surgery, discriminate and proper use is essential

Birmingham. J M SMALL

SIR —I am grateful to John Stubbs and Joe Pennybacker for stating that in a few neurological cases a "tight" brain exists even when anæsthesia seems to be perfect. I am sure everyone engaged in neurosurgical anæsthesia has encountered such cases In my experience it has occurred in patients breathing spontaneously and in patients undergoing controlled positive-negative respiration using curare—even with controlled hypotensive techniques

From my limited experience I am sure that hypertonic urea is going to be of help in these cases

Morriston Hospital,
Swansea. J M LEWIS

FLUORIDATION

SIR,—It is indeed true that the Ministry of Health Reference Note no 9 of 1955 asserted that there is "no scientific evidence that fluoride at a level of 1 part per million has any deleterious effect on the health of adults or children " A more accurate statement would be that there is no scientific evidence that it is safe to have to depend during a lifetime on water containing sodium fluoride equivalent to 1 p p m Unless and until that statement can be made, and proved, fluoridation involves imposing an unknown degree of risk upon an unpredictable number of persons for the sake of a dental benefit the amount and duration of which is seriously questioned

Doctors are entitled to ask individuals to accept risks in surgical or medical treatment, although the judgment as to whether the risk is accepted is the patient's They are not entitled to impose risks upon some persons for the benefit of others This is the fundamental objection to fluoridation.

The Ministry of Health assertion is backed up by the statement that in a community whose water-supply contained 8 p p m no important effect could be found in these people to differentiate them from those in a similar community with a low fluoride content in its water Those familiar with the literature of the subject will know that this anonymous reference is to the United States towns of Bartlett and Cameron It is rather interesting that the Councils on Drugs and on Foods and Nutrition of the American Medical Association found that there was a significant difference in the deaths and added "One might conclude that 8 p p.m of fluoride in water consumed consistently was too high a dosage for safety " It may be, of course, that the Ministry of Health does not consider death to be "an important effect "

London, S W 11 DOUGLAS OF BARLOCH

SIR,—I would hasten to assure Mr Capstick (May 28) that the Central Council for Health Education is playing a leading part in the campaign against lung cancer However its role is that of educator rather than that of a pressure group which is suggested by Mr Capstick's remarks I cannot see why there should be any competition between the reduction of lung cancer and the reduction of dental decay Surely it is our duty to promote preventive measures whenever possible whether these aim at preventing disease carrying a known fatality-rate or whether it is one which produces disability and avoidable suffering The function of this Council is to disseminate knowledge and to cultivate public opinion, including professional opinion and my letter was intended to be a reply to Mr Capstick's views on the relative importance of dental health in our community

The smoking issue seems to be an unusually large red herring containing a challenge which compels me, Sir to ask once more for the hospitality of your columns Our efforts in the field of fluoridation should not prevent us making equal efforts to prevent lung cancer In both cases the preventive measures depend upon an informed public opinion, and our resources are sufficient to tackle both problems—as well as many others

Central Council for Health Education, A J DALZELL-WARD,
London, W C 1 Medical Director

RAPID NUCLEAR SEXING

SIR —Aceto-orcein squash technique may be used for rapid nuclear sexing of oral mucosal smears Aceto-orcein, generally employed as a stain for chromosomes, may also be used to demonstrate sex chromatin

The acetic acid (45%) fixes the cells and the orcein (synthetic, 1%) stains with great clarity the sex-chromatin body which can be recognised 30 seconds after obtaining the specimen from the patient Squashing flattens the nuclei and this facilitates scrutiny of the preparation. The outstanding advantage of the method is its rapidity, and this derives from the ease not only of preparation but also of scrutiny The method is completely reliable and preparations can be made permanent if desired with little or no loss of cells

Fine details of intranuclear structure can be made out with orcein, and in the male a slim heterochromatic crescent smaller than the sex-chromatin body of the female, can be seen at the nuclear membrane The significance of this finding has still to be established

Obvious applications of this technique to nuclear sexing include the screening of large populations and the supplying of information to clinicians when this is required urgently in the treatment of individual patients

Natural History Department,
Queen's College, Dundee. ANN R SANDERSON

Parliament

Professions Supplementary to Medicine Bill

IN moving the second reading in the House of Lords on May 30 Lord ST OSWALD said that as a consequence of the report of the Simonds Committee the Government proposed at the committee stage of this Bill on June 28 to move an amendment to restore to the disciplinary committees to be set up under the Bill the express powers for the issue of writs of subpœna These were struck out at the committee stage in the House of Commons, shortly after the appointment of Lord Simonds' Committee

Lord TAYLOR said that, in the past, doctors had been in some doubt about their responsibility for the work done for their patients by these medical auxiliaries Under this Bill the position was now clear In another place, Miss Edith Pitt, speaking for the Minister, had said that in future doctors would not take responsibility nor be held responsible for work done by these new professions This was important particularly with regard to one of these professions The activities of these workers were mainly concerned with people who were not in any great danger as to life or limb, but there was one group who were handling an exceedingly lethal weapon—the radiographers, whether doing therapeutic radiology or diagnostic radiography So far as he could see this Bill transferred the doctors' responsibility to the radiographer while the radiographer was doing his job The Faculty of Radiologists had been worried about this Would it not be possible to make sure that on the board of this particular profession there could be guaranteed to be representation of at least one therapeutic radiologist and one diagnostic radiologist

Viscount SIMONDS said that the Bill established disciplinary committees with most formidable penal powers—a power to deprive a member of the particular profession, at any rate, of the best opportunities of earning his livelihood in his chosen profession. How, then, could it be just that all the available evidence should not be brought before the disciplinary committee? That was the conclusion reached by the committee on powers of subpœna over which he had lately presided, and he was pleased that the Government proposed to replace in the Bill the provision in regard to subpœnas.

On one aspect of his committee's report there had been a great deal of misunderstanding. His committee had been asked:

"To consider whether subpœnas should be issuable to secure the production before such tribunals of evidence obtained by police officers in the course of criminal investigations."

For some reason that had been thought to have something to do with telephone-tapping. Of course, it had nothing at all to do with that: it was a question whether a policeman, like any other man, should be amenable to the jurisdiction of the court and be compelled to give evidence in matters which come under his personal observation. A policeman was a civilian, if in uniform, and whether or not in uniform he should be amenable to give evidence on matters which come under his observation. That did not mean in any sense that the police authorities need volunteer information to professional bodies, or even that they need give information if asked to do so. What was meant was that a policeman who had seen or heard something which was material should be compelled to come and tell the tribunal of it. That did not mean that he might not have a good ground of privilege for refusing to give an answer. It might be that if the information he had had been obtained by telephone-tapping, that was a reason why he should claim privilege. The question was whether a policeman should be amenable to subpœna to come and give evidence. Lord Simonds believed that he should, and he hoped that there would be no qualification of any kind when this new provision was inserted in this Bill.

Royal College of Physicians of London Bill

On May 30 this Bill was read a third time in the House of Commons and passed without amendment.

QUESTION-TIME

Hospital Staffing

Mr C. L. HALE asked the Minister of Health whether he was aware that a new hospital ward in Oldham was unable to operate owing to shortage of nurses, and what steps he proposes to take.—Mr DEREK WALKER-SMITH replied: Yes. I understand that a special committee of the Oldham and District hospital management committee, which had previously been appointed to consider other matters in relation to nurse recruitment, is now considering ways and means of obtaining staff which would make possible the opening of the additional beds.

Mr JOHN PARKER asked the Minister what steps were being taken to recruit the necessary staff for the New Villas, Ockendon, and when he hoped to bring this new hospital accommodation into full use.—Miss EDITH PITT replied: All possible steps are being taken by the hospital management committee to recruit the necessary staff. It hopes to open one villa within the next month, and the remaining villas as staff are recruited and the laundry and kitchen services are extended.

Subpoena Powers of Disciplinary Tribunals

THE Government have accepted in principle the recommendations made by the Committee on Powers of Subpoena of Disciplinary Tribunals[1] and the Ministers concerned are considering the steps necessary to give effect to them. The Government are giving further consideration to a number of questions relating to the production of evidence obtained by police officers.

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[1] See *Lancet*, May 28, 1960, p. 1186.

Obituary

WILLIAM MOODIE

M.D. St. And., F.R.C.P.

Dr Moodie, consulting physician to the department of psychological medicine at University College Hospital, London, and one of the founders of the London Child Guidance Clinic, died on May 24 at the age of 74.

He was the eldest son of Robert Moodie, F.E.I.S., of Arbroath and was educated at Arbroath High School and the University of St. Andrews. He graduated M.B. in 1908 and after spending several years in the departments of physiology and pathology at University College, Dundee, he came to London in 1913 and joined the staff of the L.C.C. mental-hospital service. During the 1914–18 war he served as a pathologist in the R.A.M.C. and took part in the North Russian Expedition.

After his demobilisation he became more and more absorbed in child guidance. His opportunity came when in 1927, at the invitation of the Commonwealth Fund of America, he spent several months in the United States accompanied by two professional colleagues, an educational psychologist, and a social worker, studying the new interdisciplinary technique, preparatory to establishing the London Child Guidance Clinic as a demonstration clinic and as a postgraduate training-centre for psychiatrists, educational psychologists, and psychiatric social workers. Of this second important part of his career, K. S. writes:

"William Moodie was responsible more than any other individual for the introduction of child guidance to this country. For this task he had an unorthodox early training in physiology, clinical pathology and, then, neuropathology, from which he graduated in due course to an interest in clinical psychiatry. To meet, he was friendly though reserved, diffident, and slow-moving. He was, in fact, an intensely practical person with a life-long interest in mechanical gadgets, and a musician. Perhaps a mistrust of theory explained his somewhat cynical attitude towards abstract ideas, for he could be critical of theoretical formulations, particularly of psychodynamic hypotheses. His great strength was the interpretation of the new technique of child guidance to the medical profession and to responsible citizens, a faculty that is reflected in his published works.

"These statements do not do justice to the man, for his career is explicable only in the light of his sense of duty, and his great concern for his work and for the welfare of children. Acceptance of the Commonwealth Fund invitation meant a radical new departure for an already well-established man of 41, and took considerable courage and unselfishness. Unlike many pioneers who have risked everything in a new venture, however, Moodie remained tolerant, with a deep belief in freedom, and content to let the subject evolve.

"His advice to the Commonwealth Fund in 1939 that child guidance was not for war-time, mistaken though it appeared to many of his colleagues (including me), was made out of a deep conviction of his social duty. It was perhaps an outcome of his practical-mindedness and some lack of imagination that he failed to foresee the needs of the evacuated children, with the result that the country was less well prepared in this respect than it might have been. The same qualities led to his serving in the R.A.M.C. through the late war as a medical specialist rather than as a specialist psychiatrist. He endured the siege of Tobruk, and was evacuated only a few days before the fall—a wearing experience for a man of 56. However, he continued to serve overseas in command of the medical division in Gibraltar.

"After the war the re-establishment of child-guidance professional training was no easy task, and Moodie under-

J R Cook, D H Coombe, A S Cooper, Dorothy J Cooper, P G Cope, T B Cork, Sheila A Corrin Helena M J Cotter, J S Cox, C S D Crane, R C Crossman, F P Crowe, M F Cuthbert, B N J Daily, Faram Dastur, M J Davie, H R Davies Simon de Lange, E R Dixon, C F Donovan G A W Dove, Ewa M Dragowska, M H Draisey, B R Duncan, M W O Dunwoody, Kathleen J B Edwards, Patricia M Egan Beryl L Ellis, Mary Ellis, G J M Erwin, C E Evans, G J Evans, M D Farrar, P O Fasan, R E Faulkner, G J Fellows, J T L C Fernando, Sally E Flew, A M Fox, Janet K Gambell, Elizabeth A Gaze, D H Georgelin, Habib Ahmad Ghazi, B E Gilliver, P L Girolami, Akude Gletsu, R A Goldfinch, Mary C Goodchild, A S Gordon, Sheila E Gould, R H Grace, W R Gray, Kathleen Green, R J Green, Joan M Greenway, Mary E Gregory, J N Griffin, J B Gritton, R N Grüneberg, J H Hackwood, R M Hadley, J E Hale, G J Halls, D M Harris, Jennifer A Hartley, J M F Hartley, J M Hawkings, Ann E Haywood, Alethea B Heal, Diana P Heptinstall, R D Hill, Clare Hilton, Pauline B Hird, K E F Hobbs, D M Holmes, Sonia M Holmes, A S Horner, B L Houghton, Mary W Houlston, N M How, K E E Hubble B V Hudson, Daphne M Humphreys, Peter Humphreys, M J Hunter, Monica P Hunter, E J Igwe, R K R Innes, H G James, I M James, M L James, W F Jaworski, Jill D McK Jeffery, R W John, B D Jones, B C Jones, D A Jones, P M Jones, T M B Jones, D L Julier, C P Juniper, Brian Kell, Peter Kelly, Margaret L Kemball, R C Kennedy, Helena J T Kilkenny, Elizabeth S Kitchin, D N Landon, D A H Langman, J V Lee, Soo Chew Lee, Joan M Leese, Eva Lester, Eva H Letchner, Alan Levine, E A Lewis, D J Lightman, Chooi Cheah Lim, J D Lloyd-Still, Margaret H Lucy, J S P Lumley, Lawrence Lupin, M P McBrien, Patricia M McCormack, S J McDonald, Leonie M McEwen, M B J McGrath, Stuart McHardy-Young, Marion MacLellan, M T MacMahon, H B McMichael, Margaret R McMinn, I F Macrae, N C Malcolm, B M Male, Rosamund H Mansfield, D J Martin R C Martin R J Mason, J R Massy, A W Matthews, Labhshanker Sukhlal Mehta, B S Michaels, E H S Miles, Joyce M Miller, A J Mitchell, Michael Modell, P R W Monahan, M V Moriarty, T S Morley, A E Morris, M D R Morris, Jayne M Moses, P J Muller, J J H Mülnier, M K Murphy, J F Murray, J S Musgrove, A S Mushin, D M Muzio, May Ning, Georg Nuki, Susan T O Connor, P M Olley, E G J Olsen, M J Oliver, R H Parrott, J D Parry, S M Patient, E H M Paul, P C Pavier, Catherine S Peckham, P J Pegg, M J Pemberton, J A P Pettavel, Sally J Phillips, Dianne E Philp, Douglas Pickering, William Pickvance, J V Piper, B V Pipper, A H Platts, M S Ponnampalam, J A ffitch Pope, G M Preston, D I O Price, David Prothero, Kwamina Oboe Quansah, B J Ranscombe Donald Rau L M Razavi, Hazel L A Read, A R Reece, P M Reilly, Gunnar Reiman, P G S Relton, D A Reynolds, Felicity J M Reynolds, M T Reynolds, Janet Riddle, Christine E Riley, P A Riley, A D Rogers, Wendy Roles, A M Rose, D M Ross, M G Royle, I R Russell, Zillah A Russell, Emmanuel Urunetseyi Sagay, P E A Savage, J D Scott, Jill Sedgley, R G F L Seed Maria L Serbrock, Paul Sharpstone, D W Shedden, A J Sheehan, C M Signy, G W Simonds, Shirley K M Sinclair, Manmeet Singh, Jean A Skinner, D J Smith, M A B Sneary, Sajjan Singh Soor, Akanni Olufemi Olakunle Sorungbe, Joanna South, P E Spicer, Gillian P M Stalder, Charmian R L Stephens, F B Stephenson, Patricia S Stephenson, Anne K Stewart, Mary Stewart, Hilary Sturland, A E Stocks, D J Strath, N H Sutcliffe, J E K Tabert, D C Taylor, M E Taylor, R A M Taylor, S W C Taylor, Helen E B-L Tee, R S Terry, C H C Thomas, A J Thompson, John Thomsitt, Ada A Thornton, R H Tipton, P M J Tombleson, D A Toms, L N Travis, R R Trayner, K L K Trick, Irene J Tufft, Florence M Turner, William Ursell, Margaret R A Utudjian, Barrie Vernon-Roberts, J A S Vick, Dorothy I Vollum, B L Waldman, B A Waldron, A E Walker, Judith G Walker, K A Walker, P J Ward, D J Warren, W D N Watson, J L Wearn, P C Weaver, B R Webster, F O Wells, Tessa Westcott, Myra Wharf, W F White, Kyra A Williams, Norman Williamson, R A G d E Willoughby, B P G Windsor Manmohan Singh Wirk, J D Wonham, Bridget M Wood, Ann P Woolley-Hart, Adeline Yen

Royal College of Obstetricians and Gynæcologists

At a meeting on May 28, with Sir Andrew Claye, the president, in the chair, the following were elected to council

As representatives of the fellows John Campbell McClure Browne, Stanley George Clayton, Francis Edward Stabler, Robert James Kellar, Gavin Boyd

As representatives of the members John Stanley Tomkinson, Wallace Barr

The following were admitted to the fellowship

G H Bancroft Livingston Marjorie O Bennett, Mary A M Bigby, G W Blomfield, Joyce M Burt, W S Campbell, Edward Cope, H V Corbett, G A Craig D A Davies, Nagal Subhadra Devi J G Dumoulin, J P Erskine, J B Farquhar, G B W Fisher, A M Giles T A Gillie, A M B Grant, A St G McC Huggett, L E Hurter, D W James, Mary K Lawlor, R F Lawrence J B Lawson, D H Lees, Lorna Lloyd-Green, G I Louisson R H Macdonald, Agnes R Macgregor, K McI MacKenzie, C J Mackinlay, J T Mair, R McI Millen, Gardiner Mitchell, P R Mitchell, F L E H Musgrove, Premavathi Maddimsetti Naidu, M K O Driscoll, E R Ormerod, J H McK Pinkerton E E Rawlings, D N S Robertson, C V Salisbury, Choudhuri Abdus Samad, D A F Shaw N G G Talbot, J M Thomson, Ramsay Warden

The following were admitted to the membership

Armaity Aspandiar Anklesaria, Alison M Armstrong M P Avon, Pamela M Bacon, Amarendra Banerjee, G S Banwell J D Begg Kwesi Kobea Ogoe Bensi Enchill, Ajilady Savithri Bhandary, K G Bland, Kathleen A S Brosnan G R Brown, Solomon Burgin Biman Kumar Chakrabarti Harry Cohen J B Comerford, F G Cox, Gerda J Crow, M M de la Harpe, R A Don Sheila L B Duncan Solomon Ende, A C Fraser, P H Foote, K E Free, I K Furler, W T Gallagher, Susan George Ronald Giles, C S Harison P D Hill, Uriah Jacobson, Snehalata Bhujanga Kamath Pun Shui Kan Swadesh Kumari Kataria Brendan Keane Bhagwanti Gobindram Kotwani, Ariffin Bin Ngah Marzuki, Tarendra Nath Mitra Thomas Khoon-Fong Ng, D B Paintin, Heather M Panton Mary C W Paterson E C Pixley G L S Rankin L J Schewitz, S C Simmons Nargese Jehangir Talati E P W Tatford, Brenda A Taylor Molly E Towell Mary M Tyndall R J Venn, N F Walker, W A W Walters, D K Williams, L H Wright

University of Edinburgh

Dr Gavan Monaghan has been appointed assistant in the department of pathology

Postgraduate Medical School and Hammersmith Hospital Association

This association will hold an open day on Friday, July 8, at the hospital, Ducane Road, London, W 12 The annual dinner will be held in the evening at the Park Lane Hotel, Piccadilly

International Congress of Dietetics

This congress will be held in London from July 10 to 14, 1961 Further particulars may be had from the organising secretary of the congress, 251, Brompton Road, London, S W 3

International Congress of Neurological Surgery

This congress will be held in Washington from Oct 14 to 20, 1961 Further particulars may be had from the secretary general, Dr Bronsón S Ray, 525, East 68th Street, New York 21, New York, U S A

Road Injuries Research Group

The Automobile Association has set aside about £30,000 to finance, for seven years, a road research injuries group to be established in conjunction with the Institute of Accident Surgery at the Birmingham Accident Hospital Initially the research will concentrate on relating the injuries of car occupants to the design of their car The hospital's surgical records will be correlated with an engineer's report on the damage to the vehicle

Hospital Provident Scheme for Doctors

The Western Provident Association has introduced a special scheme for doctors and their families because some members of the medical profession feel that they do not need such extensive cover as the general public for consultant and specialist services The Association's new scheme helps them with grants for their colleagues' services The benefits for maintenance in private beds and nursing-homes are the same as for the general public Rates of subscription for the new scheme may be had from the secretary of the Association, 42, Baldwin Street, Bristol, 1

Society for Relief of Widows and Orphans of Medical Men

At the annual general meeting, on May 18, Dr W E Lloyd was elected to succeed the late Sir Robert Young as president Last year nearly £4300 was distributed to twenty four beneficiaries

Membership is open to male registered medical practitioners who at the time of election are living within twenty miles of Charing Cross Inquiries should be addressed to the secretary, Dr J A Struthers, at 11, Chandos Street, London W 1

Societe Internationale de Psychopathologie de l'Expression

The department of psychiatry of Paris University, where Prof Jean Delay and his associates have long studied psychotic art, has become the headquarters of this society Its annual conference will be held this year in Catania, Sicily, from Oct 7 to 10 Further particulars can be had from the secretary of the society, Clinique de la Faculté, Centre Psychiatrique Sainte-Anne, Paris 14, or from Dr G M Carstairs, Room 329, Tavistock House South, London, W C 1

Prof B S Platt has been appointed one of the scientific members of the reconstituted Food Standards Committee

Dr Doris McWalter, assistant principal medical officer for Glasgow, has been appointed a member of the Building Standards Advisory Committee for Scotland

The British Council for the Welfare of Spastics have published the papers on the assessment and education of children with cerebral palsy given at a conference held in Bristol in 1958 Copies (4s 6d post-free) may be had from the Council, 13, Suffolk Street, London S W 1

Living Animal Material for Biological Research —Copies of the proceedings of the symposium on this subject held in 1958 may be had from the secretary-general of the International Committee on Laboratory Animals, Woodmansterne Road, Carshalton, Surrey, England (Pp 100, £1 or $3)

The Lancet · Saturday 11 June 1960

THE GENERAL INDICATIONS FOR PSYCHOLOGICAL TREATMENT *

ALEXANDER KENNEDY
M D Lond , F.R C.P , F R C.P E , F B.Ps S
PROFESSOR OF PSYCHOLOGICAL MEDICINE, UNIVERSITY OF EDINBURGH

THE decision as to whether a patient is likely to benefit from detailed psychological treatment, with the choice of the technique most likely to succeed, is a severely practical matter Psychotherapy misapplied can be both uneconomic and harmful Any method used must, therefore, be considered with strict reference to the central aim, which is to remedy, in the individual under review, the unhappiness and inefficiency, both personal and social, which are the products of his psychological maladjustment If the subject of a psychoneurosis proves on investigation to have made an inept use of his resources and potentialities, the hope is that he may be assisted by psychotherapy to reorganise his mental economy in the interests of greater efficiency

The social structure with which so many patients are at odds owes its complexity to the development in man of the means whereby previous sensory experience can be recalled and thought about in the absence of the original stimulus, and of the development within society of the means of communication, so that one person can be influenced by the ideas of another, conveyed through the symbols of language When planning psychotherapy it should be borne in mind that the language in which the effects of experience are recorded on the tablets of the developing brain—the language of perception and of the unique inner world of the self—is not the same as the language which human beings use to communicate with one another When we try to understand or to influence another self by means of ideas, we are continually held up by the need to reformulate and translate the subjective language of recall, of feeling and of impulse into the less adequate language of words It is this process of translation more than any other factor that has divided psychotherapy into schools, each with its own interpretations of the same processes In this respect they resemble the inhabitants of different countries, living similar lives and with similar aims, yet not always able to develop the finer points of mutual understanding and sympathy through lack of a common language Since most of the controversies between schools of psychopathology are largely a matter of language, it is therefore important that, so far as is possible, psychiatrists should speak in the Esperanto of psychopathology—that is, in Plain Words, unambiguous in meaning to specialist and layman alike

It is possible, though uncommon, for one person, who is present at the right time and who utters a few words only, to alter the whole course of the thoughts and behaviour of another, who from that moment is able to bring about his own readjustment To find such words and the occasion for their use is an ideal of psychotherapeutic achievement It is, unfortunately, an ideal almost beyond attainment Yet how often, when we have been rewarded with some almost comparable experience, have we been at a loss to know quite how or why it happened unless, of course, by means of what Henry Maudsley (1886) called " a subtle collusion with the self ", which we now would call rationalisation, we can turn our wonder into triumph

We have to confess that in psychotherapy chance plays no small part and that we are at times manipulating and releasing forces which we do not fully understand In psychopathology, too, attempts are made to describe these forces in terms of systems of reference which are as purely theoretical as the cosmic explanations of the ancients Just as the alchemists of old described the reactions of chemical substances in terms of the movements of the heavenly bodies, so the psychopathologist today may be tempted to forget the extent of our ignorance, evade the effort of abstract thought, and take the easy path of the allegorical description of mental life It is tempting to accept literally one or other of the dangerously oversymbolised and oversimplified visual diagrams or blueprints of the mind which are available Celestial or genital, the symbols serve the same purpose of evading the unknown and they serve, too, to confuse the uninitiated Fortunately, just as chemistry was applied for the benefit of man even when its theoretical dynamics centred on the fallacious Phlogiston theory, so the benefits of our observation of people's psychological responses to ideas and stresses can be turned to practical account, even with a questionable theoretical basis, until science catches up Hypotheses and theories may be very valuable, provided that they never assume the status of beliefs As Appleton (1953) has said, a theory is only an hypothesis that has become respectable No-one has put this better than Sigmund Freud (1949), who was well aware of the purely empirical purpose of his constructs

> " The future may teach us how to exercise a direct influence, by means of particular chemical substances, upon the amounts of energy and their distribution in the apparatus of the mind It may be that there are other undreamt-of possibilities of therapy But for the moment we have nothing better at our disposal than the technique of psycho-analysis, and for that reason, in spite of its limitations, it is not to be despised "

If we put " psychotherapy as we now understand it " in place of " the technique of psychoanalysis ", Freud's statement of the position can give no better picture of the caretaker function of psychopathology at the present day We are likely to have the caretaker with us for a long time For even if it were possible to understand in detail the functioning of so complicated a machine as the brain, it would take a greater brain than ours to encompass its total working in one individual at one moment of time There must, therefore, be a long future for hypotheses and symbolic language with their function of enabling us to extend the reach of our abstract understanding in the same way as the symbols of mathematics take us beyond the range of present observation in the field of pure science Psychopathology is as legitimate a servant of the psychotherapist as mathematics is of the physicist, but a servant who must never be allowed to assume the mastery

The Place of Psychotherapy

Health is defined in the Constitution of the World Health Organisation as " a state of complete physical,

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* Based on a Maudsley Bequest lecture given at the Royal Society of Medicine under the auspices of the Royal Medico-Psychological Association

mental and social well-being" and this definition is defended on the score that the representatives of sixty-four governments, like the three million mothers, cannot be wrong If mental adjustment to this puristic standard of dull serenity is to be the aim of mental hygiene, it is difficult to see how psychotherapy, which is one of the most expensive forms of treatment in terms of human time and effort, can ever help us much For the moment, a simple statement of our aims in treating the individual is that we should try and deal with his maladjustment where it causes distress to himself or to those who would live in harmony with him, and to give him help until he reaches a point where he can help himself He must then learn how to live in such a way as to avoid strains with which he is inadequate to deal Physical, social and psychological treatment must thus go hand in hand, with the emphasis placed on that which is most likely to be successful We can be encouraged by the fact that our efforts will be supported by protective and compensatory mental mechanisms comparable in purpose to the homœostatic mechanisms involved in the physical defences of the organism These mechanisms have been well tried and proved in the fire of natural selection It is encouraging to remember that before the advent in medicine of specific therapies, the basis of practice was to support the natural resistance and healing forces of the body The principles of expectant treatment so ably laid down by John Hilton (1863) nearly a hundred years ago are still well worth the attention of the psychotherapist, who would be powerless were it not for the innate recuperative qualities of the human psyche Nowhere is this better seen than in psychotherapy with children who, one is tempted to think, are sometimes able to recover even in the teeth of intensive psychotherapy

In some respects psychological treatment can be compared to the medical assistance which is given in childbirth—an assistance which has also become more necessary with the advance of civilisation The fact that pregnancy must come to an end somehow is as inevitable as the fact that the maladjusted patient, as opposed to the psychotic, must after treatment continue to live in a similar world to that in which his troubles began The need in childbirth is to encourage the mother to make the best use of her own natural resources, to be able to give the right help at the right time and to reduce the incidence of complications by not interfering too much These are exactly the rules we might follow with advantage in planning psychological treatment The psychoneuroses can be looked upon as exaggerations and distortions of normal protective mental mechanisms (Kennedy 1940) In treating them our aim will always be to find the way back to a life of reasonable harmony unless serious constitutional defect or disorder of the total personality makes it necessary to lower our sights and accept an invalid adaptation

The Diagnostic Interview

The first contact which a psychoneurotic patient makes with someone who will listen to him and who shows interest and sympathy is the starting-point of a therapeutic relationship The therapeutic value of the initial consultation may be very great, especially when the doctor is the first person who has conveyed to the patient by his inquiries that the illness is not unique, that it can be understood by someone else, and that it is not a matter for self-reproach As an impression is built up of the causes of the maladjustment, of the constitutional assets of the patient, his deficiencies, and the effects upon him of stresses arising from within and without, therapeutic opportunities occur which may be difficult to reconstruct later

That the patient should be treated throughout by the doctor to whom he has first brought his troubles is an ideal state of affairs It is hoped that it will be realised more often when the medical student is taught as much about human beings as about their diseases and can be relied upon to give psychological first-aid More often than not, reference to a specialist is necessary The latter may undertake treatment himself, or he may see the patient more than once for more detailed investigation before finally making his plan If he then decides that specialised psychotherapy is necessary this may entail yet one more change of doctor

In considering the advisability of treatment by a psychotherapist who has the time and skill to carry out one of the longer methods, the consultant has certain definite responsibilities

1 He must, in giving his opinion, acquaint both general practitioner and therapist with any organic and situational factors which may influence the course of the therapy In doing so he must try to foresee any crises, such as attempts at suicide, fugues, or explosions of violence When psychosomatic disorder is present, he must arrange for coincident medical treatment, while if there are potential legal implications in the patient's behaviour the position should be clearly stated before treatment is undertaken Having thus given his own statement of the balance between consitution and stress and of the prognosis as he sees it, he must then leave the psychotherapist free to interpret the patient's needs in the light of his own inquiries

2 He must try to foresee in a general way what form of psychotherapy and what sort of psychotherapist is most likely to succeed Since the different psychotherapeutic approaches are not often specific to the types of disability which the patient may present, and are more related to his personality, there can be no question of prescribing treatment in detail Quite different approaches can be equally successful in the same sort of case, so that it must be left to the psychotherapist to adapt his own methods to the needs of the patient The diagnostic physician, therefore, needs to know the interests and special aptitudes of the therapists to whom he refers patients A skilled hynoptist, for instance, whose therapy is mainly of the imposed kind and who is helped by his firm belief in his own methods, may be excellent for a patient whose capacity for insight is small, or whose symptoms are restricted On the other hand, a realistic and self-critical patient requires a mature therapist capable of accepting responsibility for dealing with the strong transferences which are often a feature of the integrated physical and psychological treatment of, say, the intelligent depressive

3 The consultant must try to minimise the effects of the transfer from one physician to another by preparing the patient for his relationship with the therapist He must not prejudice this by rash promises, or attempt to impress his personality on the patient more than is necessary in the latter's immediate interests At the end of successful treatment, after the last interview with his psychotherapist, the patient should be saying something like this "And I'm grateful to *that chap* at the hospital—I forget his name—who sent me on to you—it seems a long time ago" This aspect of his task involves a good deal of saintliness on the part of the consultant.

Here, perhaps, an opinion may be given as to what should be the successfully treated patient's attitude to his psychotherapist When he has reached a point where his own mental powers of adjustment are adequate, he will have no further need of the therapist, who should recede quietly from consciousness, his catalytic function accomplished If they meet in the street, therefore, he might suddenly revive with slight embarrassment a train of thought that is beginning to become unfamiliar through disuse. "I am always meaning to write you a line but I never get round to it" is perhaps a good sign of a successful issue. It is a little sad that in psychotherapy, which has its share of frustrations and rewards, the doctor must resist the temptation to build a monument to his success, at any rate in the mind of the patient. Effusive gratitude too often carries with it a residuum of dependence.

Since referral to a psychotherapist implies a diagnosis of functional disorder, it is the responsibility of the diagnostic physician to put it to the patient that his symptoms are of psychological origin and to explain, if necessary, what a psychotherapist is. If the idea of treatment is not at first acceptable, it may be possible to persuade the patient at least to try the idea out. No promises should be given. The psychotherapist will be presented more often as someone "who will help you to sort out your ideas and to find out what is the matter so that you can put it right" rather than as "someone who will put you right".

Choice of Method

The question whether psychotherapy is indicated needs a clear and definite answer. Decisions on the kind of treatment, however, can be only approximate, requiring to be modified in the light of continued therapeutic inquiry. The number of variables to be considered in a diagnostic situation of this kind may, in fact, be great enough for the process of considering them to rank as an act of intuition. Psychotherapy, which can be interpreted so differently in different hands, is at least as much art as science and intuition is therefore not out of place. Semi-intuitive, therefore, though the final decision may be, it is greatly helped if in his training the psychiatrist has acquired good habits of mind and has achieved some clarity in his ideas about psychological treatment and its aims. In 1916, before the great expansion of psychotherapy, Adolf Meyer (1951) foresaw this need:

> "No field of biology is more in danger of verbosity than ours. Hence let us cultivate principles of economy. Nothing will help more towards a systematisation of a generally useful and intelligible body of facts than conscientious habits of cross-reference."

In spite of the dangers inherent in the visual representation of abstract ideas, I shall try to give some idea of the principles on which such a process of cross-reference is based. The different types of psychotherapy can be represented on a scale. Of the several parameters which might be chosen (Kennedy 1960), the one here selected is the extent to which the patient himself solves his problem or to which the solution is imposed upon him by the therapist. It is a scale of relative participation in the real work of treatment by patient and therapist. The word *work* is used because I believe that, if psychotherapy is to be successful, one or both of the parties to it must work very hard. One might put it that, if there are neither tears nor sweat in the course of psychological treatment, someone is wasting his time. On this basis, methods may be divided into:

Imposed therapies
Reconstructive counselling
Conditioning and rehabilitation
Anamnesis and abreaction
Review and resynthesis
Personal analysis and reorientation

The groups chosen are in no way mutually exclusive. For instance, imposed methods may render a patient capable of achieving a sound insight as treatment progresses.

Conditions which may Respond to Psychotherapy

The diagnostic groups cannot be placed in any constant order of amenability, for the possibility of improvement depends as much on the patient's constitution and circumstances as on the category to which his disability can be assigned. Hence, in this paper, the types of illness likely to respond to psychotherapy have been divided into a number of groups labelled according to the clinical features which can be elicited at the initial inquiry. The order in which they are given is based on the extent to which, in my experience, they have responded to psychological treatment. The groups and their order are thus inevitably personal, and modifiable in the light of the experience of others. Probably, however, they are better than no classification at all for they are intended as an aid to the planning of treatment, a mental operation which is not helped by unnecessary vagueness.

I. Acute psychological responses to stress. Panic, terror and short-term escape reactions such as amnesia.

II. Purposive functional disabilities (hysteria) when single and recent in appearance with no previous history of severe neurosis.

III. Acute tension, aggressive and protesting behaviour in childhood and adolescence. Anxiety states of recent origin.

IV. Reactive depression where the constitutional component is relatively small and the stress severe.

V. *Inefficient attitudes to the stress of physical illness, to family* and social misfortune and to endogenous depression.

VI. Organ neuroses (e.g., effort syndrome, mucous colitis, functional anorexia).

VII. Certain "psychosomatic" disorders including allergic disorders with psychological precipitants but excluding peptic ulcers, hypertension and asthma.

VIII. Failure of adaptation to cerebral deterioration and senile decline.

IX. Disorders of habit, addictions including alcoholism.

X. Obsessions and impulses if single and occurring in early life in sound personalities.

In these ten groups there is some prospect, in declining order, of wholly psychological treatment helping to bring about a satisfactory adaptation to life, in time to prevent permanent dependence. A list of conditions which are partially helped by supportive psychotherapy, or in which psychotherapy plays a minor, if essential, role, would give a very different order. Endogenous depression, for instance, although it may recover spontaneously, is not likely to do so as the result of psychotherapy alone, and physical treatment is indicated once a confident diagnosis has been made. On the other hand, the treatment of depression impersonally by physical means alone may leave the patient bewildered and with no better insight into his vulnerability to mood change than he had at the outset. For this reason psychotherapy is essential in endogenous depression but, since it is subsidiary to physical methods, it is not included.

While there are not many forms of psychiatric disorder in which intensive personal psychotherapy cannot at least comfort, it cannot be available to all, and we have to deploy our efforts where they will do the most good. The economies must necessarily be made by increasing our skill in deciding *which* patients in each group are to be given the opportunity and how much time they are to be given. In patients of poor intelligence or capacity for insight, imposed therapies such as hypnosis or direct suggestion are of most value, and without them it would be difficult to relieve the type of symptom—such as amnesia, aphonia, and mutism—which prevents communication between patient and physician (Kennedy 1940). Such treatment must be available when it is needed, and should be available for instance in hospital casualty departments (Kennedy and Neville 1957). The effects of leaving symptoms of this kind unrelieved are serious, for with each passing day the patient's escape into invalidism, often tentative at first, becomes confirmed by its success in shielding him from reality. In such cases a general psychiatrist will usually give emergency treatment himself rather than call in a psychotherapist with consequent delay. It is for this reason that the shorter methods, including hypnosis, should be included in the training and part of the armamentarium of *every* psychiatrist. The objection is often raised that purely symptomatic treatment of the imposed kind is usually followed by relapse, because it does not deal with underlying maladjustments and morbid attitudes. This is open to question in that gross hysteria is commoner in constitutionally vulnerable people in the absence of the most severe and acute forms of stress, and such patients are liable to relapse. Even the most intensive psychotherapy will not make them less vulnerable, for their problems are likely to be due to a defect in the physical substrate of mind and are *not* capable of full solution. On the other hand, there is evidence that short-term treatment may be followed by long periods of relatively good adjustment without a return of symptoms.

The Results of Psychotherapy

Assessment of the results of psychological treatment presents formidable difficulties. That the patient is delighted with the outcome may mean no more than that he has found a respectable way of rationalising an egocentricity which formerly came into conflict with his conscience. It may be that regular psychotherapy over a period of years can give some sort of purpose to a life which was formerly idle and empty. The presence or absence after treatment of symptoms complained of at the initial diagnostic interview is an unambiguous criterion if it is associated with an estimate of the patient's general adjustment to life and work and the absence of signs of gross failure such as delinquency, attempts at suicide, alcoholism or divorce. Except in conditions such as alcoholism where the simple fact that the patient is drinking/not drinking gives a direct measure of success or failure, it is difficult to apply statistics to a matter where the data are so subject to individual interpretation and bias, although the attempt has been made by several authorities (Eysenck 1952). That the use of percentages as a means of expressing a general trend can lead to absurdities in the presence of a bias of this kind is well illustrated by the evidence given to the Royal Commission on Capital Punishment (1949–53) on the results of psychotherapy in delinquents. The only safe conclusion to be drawn from recent studies seems to be that the greatest of psychotherapists, Time, in the form of the waiting-list, is successful in a surprising proportion of cases, and that patients who have attended a private analyst for some time rarely fail to conclude, if they are still attending, that it is worth their while to do so.

The conclusions which follow are personal and are not supported by statistics.

So far as *hysteria* is concerned, even if its causes lie deep, the formation of symptoms can often be prevented. The child who has been off school with a cold and who tries to get an extra day by claiming a headache is using, in a simple but not deliberate manner, a mental mechanism of escape from a civilised obligation, and the doctor who says "Nonsense, up you get" may be reversing a tendency which could be serious if encouraged by an indulgent parent, a "better be on the safe side" doctor, or a frustration-phobic psychiatrist. With hysteria "il n'y a que le premier pas qui coûte". While to the psychoneurotic with a really serious problem who presents it in the form of a conversion symptom, a moral lecture is an unhelpful affront, there are occasions when the evasion is not so unconscious as to be inaccessible to a reminder *not* to take the easy path. Certainly, in compensation cases, the course of the illness can be materially affected by the fact of who sees the patient first—a downright general practitioner or the compensation secretary of the trade union, hungry for triumphs. At the outset, adoption of the invalid attitude is usually accompanied by a phase of suggestibility which can and should be exploited while it lasts. The importance of the time-factor in early psychoneurosis was well illustrated in time of war, where a few days' delay before treating the acute breakdown made rehabilitation long and difficult. In civilian practice this is seen when the symptom is of the acute generalised kind (e.g., aphonia, mutism, amnesia, or panic state) and an insightful approach quite out of the question. The breaking down of the non-realisation barrier is then a matter of urgency. Among the methods which can be used is hypnosis. As the method which opened the door to the possibilities of psychological treatment, in the hands successively of Charcot, Bernheim, Liebault, Janet, Breuer and Freud, it has the sanction of history. It requires no preparation or apparatus and is therefore ideal for the functional emergency. Admittedly, we do not know how it works, but this applies to a great deal that happens in the therapeutic relationship. The fact that hypnosis has often been used by charlatans may give it a bogus air, but medicine has had to incorporate into its professional practice much that started in the market-place.

Where anxiety is nearer to the surface, cathartic methods will often bring some relief, but in some quarters the idea dies hard that abreaction should be made an object in itself. The main function of abreaction in the course of psychotherapy is to bring new material to the surface so as to allow patient and physician to assess its importance. The relief it brings is rarely permanent if the subsequent work of resynthesis is not taken up. In the case of *obsessional states*, a great deal of the psychotherapy that has been given has probably been wasted, for the long-term results are now known to be poor. The fallacy in treating obsessional states has been the belief that if psychopathological material of great interest and richness keeps appearing at the interviews, with strong abreaction, the patient will necessarily benefit. A common sequence in cases of obsession is that the appearance of symbol-rich material, often elicited with suspicious ease, is followed by great relief for a week or two. Patient and therapist then seek in vain to produce the same effect once more. Months or years after he has been abandoned in despair, the patient may be found to have recovered spontaneously, or the organic state or functional psychosis of which the obsessions were a symptom may have revealed itself.

It is often forgotten that even where *anxiety* is the most prominent feature, there is a major place for psychotherapy in which the place of emotion is secondary to a simple conscious discussion of the patient's immediate problems. Here the patient may be compared with a bankrupt whose business has failed from a combination of bad luck and bad management. He agrees to the appointment of a receiver who may be able to come in and keep the business going and help him, the proprietor, to get it on its feet. Old problems are seen through new and experienced eyes as the patient helps the therapist to make a detached reconstruction of the situation. Here abreaction is only an incident and extremes of transference can quite reasonably be discouraged lest their resolution add too much to the length of treatment. This type of therapy, with its physical and social supporting measures, is the bread-and-butter of the psychiatric clinic It is particularly applicable to problems created by physical disease, and it is a kindly approach, for instance, to the elderly patient who is finding difficulty in accommodating himself to his failing powers In psychotherapy the role of reason need not always, as a matter of principle, be subordinated to that of emotion, especially as a logical sequence enables patient and physician to keep the final aim in view The fact that his work involves the manipulation of emotion and impulse does not absolve the therapist from planning his actual practice in a systematic way

It is often thought that the application of psychotherapy to *high-grade mental defectives* is hardly worth while Though the extent to which they can acquire an intellectual appreciation of their problems must be limited, this is not the same thing as absence of insight, and the latter is often, in terms of their own mode of thought, surprisingly good The handicapped child who is brought up in an institution, and who in adolescence is turned out into a world whose written symbols he cannot interpret and whose customs are beyond his comprehension, is sometimes friendless and bewildered except when working in the task for which he has been trained. His chance of gaining the daily petty triumphs which sustain the average man is limited. The inability to keep his end up, to develop a sense of humour, or to understand abstract principles and conventional ideals, which are the penalties of his handicap, are complicated by the absence of a background of the normal affective relationships of childhood. Yet, if his language is understood, he is intensely rewarding as a patient because his demands are simple

The Salvation Army have long known how to present the aims of life to the backward and to give them a sense of equality in the sight of God. They have thus had an enormous influence in preventing the backward from taking the foresightless path of delinquency The psychotherapist must follow their example and learn to use the language of the backward if he is to restore to them a sense of security in their relations with their fellow men

Psychoneurotic Symptoms with Organic Nervous Disease

One of the products of increasing knowledge of the effects of organic brain disease on the function of the psyche is the recognition not only that structural change often seems to predispose the individual to psychoneurotic reactions, but that it is often complicated by a functional overlay due to failure to adjust to the neurological handicap In senile and arteriopathic dementia, and especially in the presenile deteriorations, pathological mental mechanisms of a very simple kind are frequently seen and if the dual nature of the process at work is understood, psychotherapy is remarkably effective, even though it may have to be superficial and didactic. The so-called degenerative hysterias found in association with chronic encephalitis, epilepsy, disseminated sclerosis, or other chronic processes, with their gross functional symptoms and childish behaviour, are remarkably easy to treat by direct suggestion and regime. The didactic approach appeals to the "concrete attitude" which so often develops in the course of organic brain disease.

In *psychosomatic disorders*, if exclusive stress is laid on purely psychological factors and the importance of organic predispositions and precipitating factors is ignored, mistakes will inevitably be made. The large-scale treatment of effort syndrome during the war did a great deal to convince physicians of the possibilities of the psychological approach and the increasing knowledge of the neuroendocrine links between mental stress and its somatic counterparts provide a rationale for further development in this field But it is essential that anyone who undertakes treatment even of such conditions as da Costa's syndrome, functional indigestion, mucous colitis, eczema and enuresis, with their obvious psychogenic elements, should be fully aware of the physiology of the processes of which they are pathological caricatures These often prove to be somatic "fractionations" of the anxiety syndrome and, as they are usually determined by conflicts of a kind not difficult to bring to the surface, treatment often has very satisfactory results The same cannot be said of the treatment of hypertension, or of gastric ulcer, which, although obviously influenced in their course by psychological factors, are very uncertain in their response to psychotherapy Those who advocate full psychoanalysis for these disorders seem to be motivated more by faith in the method than by any study of the results

The psychotherapy of *delinquents* brings into relief a special problem that exists elsewhere in psychotherapy as well As physicians we are concerned with the mental health of each patient as an individual, and as citizens we are concerned with the influence of his illness on others and on society Where the aims of treatment in the two fields cannot be achieved in the same operation we sometimes have conflicts of our own to solve as to what extent must we expect society to adapt to the patient and to what extent must we adapt the patient to society No delinquent can be considered out of his environment so that the therapist who chooses to treat him must know something of the background and the language of the antisocial. Older but well-tried methods of approach—penal sanctions and religious influences, for instance—are not to be set aside at once because the present trend is psychodynamic The therapist cannot afford to isolate or overprotect his patient, but must keep him in contact with society so that its influence and its sanctions can be felt at all levels of his mental life, conscious and unconscious

The Patient who Asks for Psychotherapy

From time to time we have to consider how far the patient's own request for psychological treatment is an indication of his need for it If cure is improbable, the amount of a physician's time which should be spent on consolation is a matter for the individual, provided that the application of comfort does not delay other necessary treatment. We must realise with Sophocles' Ajax that "it is not the part of a sound physician to wail incantations over a lesion that calls for the knife", for the request for a gentler approach may be the patient's personal defence against the realisation that something more serious is amiss The way in which an intelligent prepsychotic will sometimes welcome a diagnosis of psychoneurosis and submit himself to treatment suggests the avoidance of a painful insight Like the patient who has learnt that his malignant disease is inoperable and who has developed an intense belief in divine healing, it is not treatment that he seeks but magic, and psychiatry must often disappoint by offering the staff of Æsculapius to those who would prefer the wand of Merlin Comforters, too, like indulgent parents, may render the comforted less sensible to their obligations to others In some contemporary cultures the patient with means can buy psychotherapeutic cheer as he might buy alcohol, and the longer and gentler methods are sometimes used for no other purpose than to provide companionship with discussion of the patient's own favourite topic, himself Those who demand and receive such treatment are customers rather than patients, and its provision is no part of medical psychotherapy which subscribes to the Hippocratic ideal

Nevertheless there are many who, while not in serious danger of breakdown, have pressed on too fast in search of their immediate goals and who realise that they must now look back and come to terms with the forces which drive them and allow the following shadow of themselves to catch up with the substance For, as Lucretius observed long ago

> " So each man strives to flee that secret foe
> Which is himself But move he swift or slow
> That self forever punctual at his heels
> Never for one short hour will let him go "

In general, the patient who is worried and who is prepared to make an effort, if only he can learn the kind of effort to make, is worth a more personal approach than the one who wishes to leave the whole matter to the psychotherapist On the whole, the patient who asks for psychotherapy deserves to have his claims carefully examined, for his request may be both a symptom of disorder and a signal of distress

The Individual Approach of the Psychotherapist

When he is actually engaged in psychotherapy, the physician's attitude of mind has to be very different from his critical objectivity at the diagnostic stage If his role is to carry conviction with the patient, he must believe in what he is doing, and it is quite reasonable for him to choose some system or frame of reference to simplify his tactical thinking at the time But the therapist who will use only his own method, in the face of symptoms requiring imposed psychotherapy or drug treatment, is comparable to a sportsman who will not shoot a sitting bird even though he and his party are starving The treatment of illness is too difficult and serious a matter to be regarded as a sporting contest Psychotherapy is real life, and those who employ it must use every means they can command against the common enemy They may have to believe that no situation is hopeless Marshal Foch's (Aston 1929)

> "Mon centre cède, ma droite recule, situation excellente J'attaque!"

is in the very spirit of active psychotherapy Although there seems to be little objection to the psychotherapist aligning his practice with that of a particular school, or on the other hand trying to make use of those features which he considers most useful in each, there can surely be no good reason for the confusion of systems and terminologies which is to be found One sometimes encounters a sort of bewildered and polyglot eclecticism which expresses itself in mixed metaphors and descriptive terms, euphonious enough if said quickly, but at which the mind boggles if it seeks their abstract meaning " Psycho-allergy " and " a hernia of the unconscious " are early examples " Guilty feedback " and " abreaction at the diencephalic level " are more up-to-date specimens

Psychotherapy is, apart from the few specific treatments in psychiatry, still the most potent force we possess for both cure and comfort It is hard work, does harm less often than most forms of treatment, and is often strikingly successful A psychotherapist must be prepared to identify himself very fully with the life and interests of his patient, must be nimble in penetrating his defences and evasions, and must be quick to learn his language His work is to treat and not to judge, and it must not upset him to realise that his patient in many respects may be a better man than he Most important of all, he must know when to stop and learn how to leave his patient content to be no more than Nature made him

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PHENMETRAZINE HYDROCHLORIDE AND METHYLCELLULOSE IN THE TREATMENT OF "REFRACTORY" OBESITY

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To lose weight obese people must reduce their caloric intake to a level much below their current energy expenditure Many, however, are either unable or unwilling to curb their appetites sufficiently, despite continued dietetic advice and encouragement Too often their despairing medical attendant feels obliged to prescribe some drug for them—as an adjunct to dietetic advice—in the hope that it may reduce their appetite

Thyroid preparations are valueless in the treatment of obesity (Edwards and Swyer 1950), except when there is coincident hypothyroidism Amphetamine or dexamphetamine sulphates *B P* are still often prescribed to suppress excessive appetite, though they may not be entirely free from the dangers of habituation and toxicity (Aldersberg and Mayer 1949)

Two preparations more recently recommended as adjuncts to dietary treatment are phenmetrazine hydrochloride ('Preludin') and methylcellulose ('Celevac') The former is said to possess the appetite-reducing powers of the amphetamines without their undesirable attributes Methylcellulose is an inert indigestible substance which swells up in the stomach and small

TABLE I—DATA CONCERNING THE THREE GROUPS OF PATIENTS

—	Group A	Group B	Group C
No of patients			
Totals	25	32	28
Females	22	28	24
Males	3	4	4
Diabetics			
No *	15 (*4*)	15 (*3*)	17 (*3*)
Age (yr)	59·2 (*39–72*)	56·8 (*38–78*)	58·0 (*32–74*)
Body-weight (lb) †			
1 yr before trial	183·2±16·6 (*156–209*)	187·8±22·8 (*153–251*)	187·7±18·7 (*156–232*)
Change in yr preceding trial	+1·1±8·6 (*−15–+19*)	−0·7±7·9 (*−12–−17*)	−1·8±6·0 (*−10–−9*)
At start of trial	184·3±16·0 (*162–218*)	187·1±19·7 (*156–242*)	185·9±17·4 (*162–224*)
" Standard weight " ‡	144·1±9·7 (*131–178*)	141·4±7·5 (*121–162*)	144·1±8·7 (*132–169*)
Wt at start of trial as % of standard	128·1±9·9 (*115–155*)	132·1±11·9 (*117–164*)	129·5±13·1 (*115–156*)
Excess wt at start of trial	40·2±13·6 (*22–74*)	45·7±16·6 (*23–80*)	41·8±18·1 (*20–75*)

* Numbers in parentheses are those taking insulin.
† Values are means, standard deviations, and ranges
‡ Standard weight for each patient was derived from tables of the U S.A. Medico-Actuarial Investigation, New York, 1912

intestine and thus, if taken with water before meals, might produce a sense of repletion

We report the results of a controlled double-blind trial of phenmetrazine and methylcellulose as adjuncts in the treatment of obese outpatients whose obesity had proved refractory to routine dietetic advice

Methods

The records of the dietetic outpatient department were searched for patients treated for obesity over the previous year who had failed to lose weight in the past three months, despite the prescription of reducing diets providing 1100–1600 Calories a day The first 92 patients who satisfied this criterion were taken 5 were rejected because they were not sufficiently overweight 2 more had to be withdrawn during the trial 1 became pregnant, the other developed hypertensive heart-failure All the remaining 85 were visibly obese, the obesity of 47 was, not unexpectedly, accompanied by mild diabetes, but only 10 were taking insulin, the small dose of which was not altered during the trial They were divided into three deliberately matched groups (A, B, and C), none defaulted from the trial The essential facts about these patients are set out in table I

Initial Procedure

The patients were invited to attend special sessions of the clinic reserved for the study Their previous clinical history and present physical status were recorded, blood glucose and cholesterol levels were determined They were weighed in indoor clothing on a regularly standardised lever-type balance

The actual diet being eaten by each was assessed from the dietary history, which was subsequently cross-checked independently by two or more dietitians, only a few frankly admitted to eating much more than the diet allowed All were then reinstructed in the diet previously prescribed, exhorted to adhere to it, and told that they were to be given some tablets which might or might not assist them to do so

Tablets Administered

These were of 4 kinds

(1) Pink-coloured tablets each containing 0·5 g of methylcellulose Three of these were taken three times daily with a glassful of warm water half an hour before each of the three main meals

(2) Dummy tablets made of lactose of the same size, shape, and colour as (1) and taken in the same way

(3) Small white tablets each containing 25 mg of phenmetrazine hydrochloride During the second stage of the trial (period 2, table II) the patient was instructed to take one twice daily with a glassful of warm water half an hour before breakfast, the midday meal, or the evening meal, depending on which were the two largest meals The second dose was never taken later than 6 P.M Later in the trial (period 3, table II) one tablet was prescribed three times daily before each main meal

(4) Dummy lactose tablets identical in appearance with (3), and taken in the same way

Conduct of Trial

Each patient was weighed at fortnightly intervals and afterwards interviewed by one of us (L J P D or A P M), the purpose being to stress the importance of losing weight and of keeping to the diet. At each attendance the patients were given only enough of the appropriate tablets to last until the date of their next visit, but again without any promise of their efficacy The trial was divided into three periods as follows

Period 1 (4 weeks)—All the patients received dummy tablets, simulating either methylcellulose or phenmetrazine, to assess the possible influence of special attention and new treatment in encouraging them to adhere more strictly to their diets

Period 2 (8 weeks)—The patients in groups B and C were given active methylcellulose and phenmetrazine respectively, while those in group A continued to take one or other of the two kinds of dummies This change was carried out by one of us (K R) without informing either the patient or her medical colleagues (L J P D and A P M.), who were unaware of the group to which each patient had been assigned or of whether any one patient was receiving active or dummy tablets In this way a " double-blind " trial was assured, and the response to treatment could be assessed without prejudice born of pre-knowledge of the medication given

Period 3 (8 weeks)—A few days before the end of period 2 a preliminary analysis of the data was made by one of us (L J P D) without disclosure of the identity of the patients This showed that methylcellulose was having little effect—in contrast to the phenmetrazine—on the weight of the patients The original plan to give patients in group A active phenmetrazine or methylcellulose and those in groups B and C dummy methylcellulose and phenmetrazine respectively was altered, patients in groups A and B were instead given active phenmetrazine However, all patients in group B and half of group A had been taking active or dummy methylcellulose and would therefore appreciate that they were being given different tablets Therefore half of those in group C were given dummy phenmetrazine and the remainder dummy methylcellulose tablets so that any effect of a recognised substitution would be revealed These substitutions were again made by K R

TABLE II—INFLUENCE OF ADMINISTRATION OF THE SEVERAL PREPARATIONS ON THE BODY-WEIGHT (LB) OF THE THREE GROUPS OF PATIENTS (VALUES ARE MEANS, STANDARD DEVIATIONS, AND RANGE)

Period	—	Group A	Group B	Group C
	Initial weight	184·3±16·0 (*162–218*)	187·1±19·7 (*156–242*)	185·9±17·4 (*162–224*)
1	After 4 weeks administration of	Dummy phenmetrazine or dummy methylcellulose	Dummy methylcellulose	Dummy phenmetrazine
	Weight	182·8±17·0 (*159–219*)	186·1±20·6 (*158–243*)	185·9±18·0 (*159–225*)
	Change in weight	−1·5±2·9 (−11–−3)	−1·0±2·9 (*−7–−5*)	0±2·1 (*−5–−4*)
2	After 8 weeks' administration of	Dummy phenmetrazine or dummy methylcellulose	Active methylcellulose	Active phenmetrazine
	Weight	182·6±18·0 (*155–219*)	185·5±20·3 (*158–244*)	179·9±18·4 (*151–217*)
	Change in weight	−0·2±2·7 (*−8–−3*)	−0·6±4·1 (*−13–−7*)	−6·0±3·2 (*−13–−1*)
3	After 8 weeks administration of	Active phenmetrazine	Active phenmetrazine	Dummy phenmetrazine or dummy methylcellulose
	Weight	178·5±17·6 (*152–216*)	182·7±21·5 (*155–255*)	181·9±17·4 (*152–220*)
	Change in weight	−4·1±4·6 (*−20–+7*)	−2·8±5·3 (*−13–−11*)	+2·0±3·2 (*−6–−8*)

Results

Changes in Weight

Table II sets out the changes in weight. In period 1, when all the patients were receiving dummy tablets, only a few lost weight. In period 2 there was little weight change in most of those receiving methylcellulose (group B) and those continuing to receive dummy tablets (group A), whereas there was a mean loss of 6.0 lb. in the patients receiving phenmetrazine hydrochloride (group C). This loss was statistically highly significant ($P<0.01$) by comparison with that of the other two groups in the same period.

In period 3, those who had lost weight while receiving phenmetrazine (group C) showed a mean gain of 2.0 lb. when returned to dummy tablets. Those who had failed to show a significant mean loss of weight in the previous eight weeks when taking dummy tablets (group A) or methylcellulose (group B) now showed a mean loss of 4.1 lb. and 2.8 lb. respectively, when transferred to phenmetrazine. The mean weight gain of those in group C was statistically highly significant by comparison both with their mean weight loss in the previous eight weeks and with the mean weight losses of groups A and B in period 3 ($P<0.01$). The weight losses of those in groups A and B also differed significantly from their losses in the previous eight weeks ($P<0.01$).

During period 3 the mean weight loss (−3.6 lb.) of those in group A who had previously been taking the dummy methylcellulose, and had thus been aware of the change in tablets, did not differ significantly from that (−4.5 lb.) of those previously taking dummy phenmetrazine and who did not notice any change in medication. Similarly there was little difference in the weight changes between those in group C who were given methylcellulose (−1.7 lb.) and those given phenmetrazine dummy tablets (−2.3 lb.).

The mean weight loss of groups A and B when given phenmetrazine in period 3 was less than that of group C given the same compound in period 2, although the latter were taking a smaller dose (25 mg. twice daily as opposed to 25 mg. three times daily). There are several possible explanations of this. The trial began towards the end of May, 1957; period 3 was thus in the autumn and many patients had begun to wear heavier clothing. They were also likely to be consuming more calories, perhaps because the weather was colder, but more probably because non-fattening vegetables and other seasonal low-calorie foods were now more expensive and difficult to obtain. Moreover their interest in the study and their very limited initial enthusiasm for dietary discipline had noticeably deteriorated.

Other Changes

Blood-pressure was checked regularly; no important alterations were observed. Of the 28 patients in group C, however, 8 showed an apparent fall both in systolic and diastolic pressure after receiving phenmetrazine for eight weeks (end of period 2), by comparison with the initial blood-pressure at the start of the trial. None in this group showed any rise in blood-pressure.

The *blood glucose and cholesterol* levels changed considerably in some patients during the trial. However, there was no consistent trend, either up or down, nor any apparent relation to losses or gains in weight.

Symptoms and Side-effects

Any subjective effect attributed by the patients to the tablets was noted, but, apart from asking whether they felt less hungry or more able to adhere to the diet, direct inquiry for side-effects previously reported in published accounts was especially avoided.

48 patients noticed no effects from taking any one of the four different preparations given. Only 5 said that they felt less hungry; they were taking phenmetrazine at the time. 2 patients felt more hungry on methycellulose, and another complained of nausea. Generally the change from dummy to active tablets and vice versa went unremarked by the patients, though some who chewed rather than swallowed their tablets noticed the bitter taste of phenmetrazine and the difference in consistence between dummy and active methylcellulose.

Of the 57 patients receiving phenmetrazine thrice daily (period 3) 5 complained of insomnia, while 7 others complained of some headache, lightheadedness, dizziness, nervousness, or excitability; 9 patients receiving dummy tablets had similar complaints but not insomnia. Consequently with the exception of insomnia following an evening dose of phenmetrazine, little significance can be attached to these symptoms.

Several patients assured us that they felt better as a result of taking the tablets, though sometimes it subsequently transpired that they were taking dummy tablets at the time. No distinct stimulation or euphoria was noted in those taking phenmetrazine.

2 patients, after taking phenmetrazine for six weeks, complained of palpitation and a return of previous angina pectoris. These complaints ceased when this medication was subsequently stopped.

Discussion

Under the conditions of this trial phenmetrazine effected a statistically significant mean loss of weight in obese patients whereas a preparation of methylcellulose had no such effect.

Both preparations were given a very severe test. An attempt to treat the patients by conventional dietetic advice over the previous year had been unsuccessful, and none had lost weight in the past three months. Moreover, their mean weight loss in the first month of the study when dummy tablets were given was negligible. Although weight loss by dietary restriction may be delayed for several weeks, those in groups A and B showed no substantial loss in the first three months of treatment. The patients were therefore not much influenced by the increased attention or the giving of tablets; their obesity may well be described as refractory.

Dexamphetamine, in similar short-term studies, promoted a weight loss of about the same amount (Edwards and Swyer 1950) and its undesirable attributes may be unduly emphasised. We know of no evidence that amphetamine or dexamphetamine sulphates are less effective than phenmetrazine, which is three to six times more expensive. In Scotland the cost to the National Health Service of dispensing, on prescription, 100 tablets of these preparations is as follows:

Preludin tablets, 25 mg.	18*s.* 3*d.*
Tab. amphetamine sulphate *B.N.F.* 5 mg.	3*s.* 5½*d.*
Tab. dexamphetamine sulphate *B.N.F.* or *B.P.C. addendum* (1954) 5 mg.	2*s.* 9½*d.*
Dexedrine tablets, 5 mg.	5*s.* 8*d.*

It is remarkable that so few (5 of 85) patients admitted that they had less desire for food when taking phenmetrazine; the compound is considered either to inhibit appetite or to produce early satiety. However, Edwards and Swyer (1950) found that dexamphetamine seldom diminished subjective feelings of hunger in obese patients who lost weight when taking it

In this trial phenmetrazine produced no important side-effects except insomnia when taken in a dose of 25 mg thrice daily This is in keeping with previous reports (Martel 1957, Barnes 1958) However, 7 patients have since asked for a renewed supply of the drug, which raises the serious question of addiction Kahan and Mullins (1958), Evans (1959), and Glatt (1959) have all described patients, not previously psychotic, who began taking phenmetrazine tablets for slimming but afterwards used them as " pep pills ", gradually increasing the dose up to 20 tablets (0 5 g) or more a day They developed a psychotic schizophrenic type of illness, often associated with delusions and hallucinations, lasting weeks or months, resembling the psychosis caused by addiction to amphetamine Incidentally the cost of the pills can lead to poverty and consequent ruin

It must be stressed that the phenmetrazine was given for periods of only two months and that the weight loss, though statistically significant, was disappointingly small There is still no acceptable evidence of the efficacy of phenmetrazine given for longer periods Prolonged studies have, however, shown that in the long run obese patients treated with amphetamine or dexamphetamine and diet lost no more weight than those treated with diet alone (Aldersberg and Mayer 1949) There is no reason to expect long-term treatment with phenmetrazine to be any better

It has been suggested that about a quarter of patients given phenmetrazine for two months or so become accustomed to food restriction and thus have no further need to take the drug (Martel 1957) The mean gain in weight of patients in group C during period 3 does not support this view

Summary

A double-blind clinical trial of methylcellulose and phenmetrazine hydrochloride was carried out on 85 obese outpatients who had proved refractory to dietary advice alone

Methylcellulose was ineffective. Phenmetrazine hydrochloride produced a very small, but statistically significant, mean loss of weight in two months

No important side-effects resulted from the use of phenmetrazine hydrochloride in a dose of 25 mg twice daily 5 patients complained of insomnia and 2 of a return of angina pectoris when the dose was 25 mg thrice daily

Because of its cost, its small influence on appetite, and the dangers of addiction, we do not regard phenmetrazine as a good drug for the routine treatment of obese patients

We thank Sir Derek Dunlop for his encouragement and advice, and Miss E M Wilson and Miss E N Owles for much help with the dietetic interviews Harker Stagg Bros supplied the methylcellulose in the form of 'Celevac' tablets with dummy tablets to match The phenmetrazine hydrochloride ('Preludin') and matching dummy tablets were provided by Pfizer Ltd and Boehringer Sohn

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PHENMETRAZINE AND DEXAMPHETAMINE IN THE MANAGEMENT OF OBESITY

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While nobody seriously doubts that obese patients will lose weight when their intake of food is sufficiently curtailed, there is much difference of opinion as to the most satisfactory way of restricting the amount of food that they eat Apart from the large variety of special diets in use, a number of drugs have been proposed as aids to weight reduction, in the belief that, if appetite could be depressed by this means, weight might be lost more consistently and more rapidly than is usual with conventional methods

Amphetamine and *d*-amphetamine have been used for the suppression of appetite for many years, phenmetrazine ('Preludin'), an analogue with reduced sympathomimetic properties, was introduced in 1954 by Thomae and Wick for the same purpose So far as we are aware, no direct comparison has been made of the value of phenmetrazine and *d*-amphetamine in the management of obesity We now report the results of such a clinical trial, which also includes a comparison of the effects of these two drugs with those of inert tablets

Methods

A " double-blind " procedure was used, so that the identity of the drug in use was unknown to the patient and to the doctor, and remained so until the conclusion of the trial Three series of tablets of similar appearance were made up as follows phenmetrazine hydrochloride 25 mg, dexamphetamine sulphate *B.P C* 5 mg, and a control tablet consisting of lactose, talc, starch, quassia, and magnesium stearate. A " cross-over " technique was employed in the administration of the tablets (Gaddum 1953), so that each patient received all three forms of treatment, in this way it was hoped to reduce errors due to differences in the response to each drug by individual patients

Any patient referred to the dietetic department on account of obesity was accepted for study, provided they were considered to be sufficiently obese to justify the imposition of a dietary regimen providing 800–1000 calories for a period of eighteen weeks, and that their circumstances would allow them to attend the department regularly once a week for weighing All were treated as outpatients, and they were advised to remain on the same diet throughout the investigation A conventional reducing diet was prescribed which provided between 800 and 1020 calories daily according to the initial weight of the patient, consisting of carbohydrate 75–90 g, protein 45–52 g., and fat 38–50 g approximately Patients were instructed to take one of the tablets with which they were supplied half an hour before breakfast and half an hour before their midday meal

All patients were treated for three consecutive periods of six weeks with one of each of the three types of tablet throughout each period. The order of administration of the tablets was determined before the beginning of the trial by preparing a table based on random numbers (Bradford Hill 1955), so that the sequence of administration of each drug was varied in a random manner

Results

51 patients were accepted for the trial, and of these 37 completed the full period of study lasting eighteen weeks Of these 37, 8 were males (average age 59 6 years, range 45–70) and 29 were females (average age 50 1 years, range 21–69)

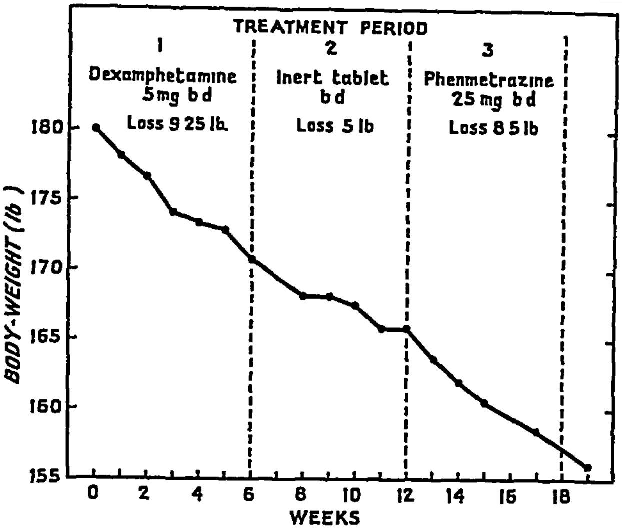

Fig 1—Typical example of results

The patient was a 56-year-old woman, height 5 ft 8 in, ideal weight 140 lb on a diet yielding 1018 calories a day

A typical example is illustrated in fig 1

The patient was approximately 40 lb overweight when first seen She was treated with dexamphetamine, inert tablets, and phenmetrazine in that order, each for a period of six weeks During the first period she lost 9·25 lb (4·20 kg) in weight, in the second period 5·0 lb (2·26 kg), and in the final period 8·5 lb (3·85 kg)

The results obtained in the three treatment groups, irrespective of the order in which the drugs were given, are shown in table I The mean weight loss during six weeks' treatment with inert tablets was 4·76 lb (2·16 kg), with phenmetrazine 8·26 lb (3·74 kg), and with dexamphetamine 6·7 lb (3·04 kg)

TABLE I—LOSS OF WEIGHT DURING TREATMENT FOR PERIODS OF SIX WEEKS

—	Treatment		
	Inert tablets	Phenmetrazine 25 mg b d	Dexamphetamine 5 mg b d
No of patients	37	37	37
Mean loss of weight per patient in 6 weeks (lb)			
Amount	4·76	8·26	6·71
Standard error	±0·71	±0·70	±0·67
Range (lb)	14·5–−4·0	18·0–1·0	19·5–−3·5

Analysis shows that the difference between the mean loss of weight during treatment with phenmetrazine and with inert tablets is highly significant, the difference between the mean loss of weight on inert tablets and on dexamphetamine is less, though still significant Although the mean loss of weight during treatment with phenmetrazine is greater than with dexamphetamine, analysis shows that the difference between the means is not statistically significant

In table II the results have been arranged to demonstrate the striking effect of time on the loss of weight, irrespective of the identity of the drug in use It is apparent that the loss of weight during the first period of six weeks is much greater than in either of the two succeeding periods

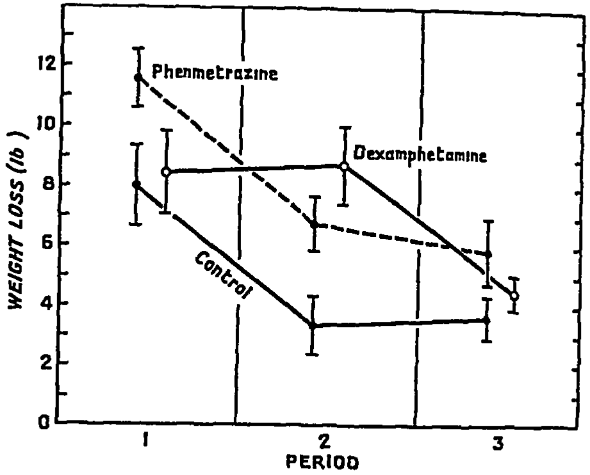

Fig 2—Relation between drugs used and loss of weight in three successive periods of six weeks each (plotting-points show mean and vertical lines standard error)

The number of patients receiving each drug in each period, together with the mean loss of weight per patient during each period of treatment, is shown in table III

TABLE II—LOSS OF WEIGHT DURING THREE SUCCESSIVE PERIODS, EACH OF SIX WEEKS, IRRESPECTIVE OF DRUG USED

—	Period		
	1	2	3
Mean loss of weight per patient per period (lb)			
Amount	9·43	5·59	4·72
Standard error	±0·74	±0·70	±0·48
Range	19·5–1·5	14·5–−4·0	12·5–−3·0

Analysis of significance of difference between means

Period 1 *v* period 2 t=5·12 (P<0·001)
Period 2 *v* period 3 t=1·09 (0·3>P>0·2)

Since the precise effect of a treatment depended upon two things—namely, the kind of tablet taken and whether it was administered in the first, second, or third period—a more accurate judgment can be made if these two influences are disentangled The regression of weight loss upon period of treatment proved not to be significantly different for the three kinds of tablet, so a common set of correction terms could be used These were

First six weeks	−2·85 lb
Second six weeks	+0·99 lb
Third six weeks	+1·86 lb

When these correction terms are applied to the weight losses of the individual patients, the influence of period of treatment is counteracted, at any rate to a first approximation Table IV gives the mean differences in the weight lost with and without the correction for the period of treatment Although in two cases the correction slightly decreases the difference observed, the statistical significance of each difference has been appreciably

TABLE III—NUMBER OF PATIENTS AND MEAN WEIGHT LOSS IN EACH TREATMENT GROUP

—	Period 1			Period 2			Period 3		
	Inert tablets	Phenmetrazine	Dexamphetamine	Inert tablets	Phenmetrazine	Dexamphetamine	Inert tablets	Phenmetrazine	Dexamphetamine
No of patients	11	14	12	17	12	8	9	11	17
Mean loss of weight (lb) per patient per period of 6 weeks	7·9	11·5	8·4	3·3	6·7	8·7	3·6	5·9	4·5

TABLE IV—MEAN DIFFERENCES BETWEEN THE AMOUNT OF WEIGHT LOST DURING SIX WEEKS' TREATMENT WITH THREE DRUGS, BEFORE AND AFTER CORRECTION FOR THE ORDER IN WHICH THE DRUGS WERE GIVEN TO INDIVIDUAL PATIENTS (SEE TEXT)

—	Mean difference (lb)		
	Inert tablets *v* phenmetrazine	Inert tablets *v* dexamphetamine	Dexamphetamine *v* phenmetrazine
Uncorrected	3 507	1 926	1 378
Corrected	3 262	2 008	1 192

Analysis of Significance of the Differences between the Means

	Uncorrected	*Corrected*
Inert tablets *v* phenmetrazine	t=3 84(P<0 001)	5 28(P<0 001)
Inert tablets *v* dexamphetamine	t=2 05(0 05>P>0 02)	2 53(0 02>P>0 01)
Dexamphetamine *v* phenmetrazine	t=1 57(0 2>P>0 1)	1 76(0 1>P>0 05)

TABLE V—WEIGHT LOST BY 14 DEFAULTERS WHILE THEY REMAINED UNDER OBSERVATION

—	Inert tablets	Phenmetrazine 25 mg b d	Dexamphetamine 5 mg b d
Mean weight loss (lb) per patient per period of 6 weeks	4 2	9 0	6 0

increased by the removal of the effect of the order in which the treatments were given

The results obtained in patients who failed to complete the eighteen weeks of study have not been taken into account in preparing tables I–IV These results have been summarised in table V

In fig 2 we have summarised the results obtained with the three types of tablet in each period As treatment continues, the amount of weight lost with each type of tablet is steadily reduced, and after twelve weeks the difference between the three becomes very small

Discussion

This trial was designed to show whether two of the drugs commonly recommended in the management of obesity had any advantage over dietary restriction alone in ensuring or increasing loss of weight, and also to compare the relative efficacy of these two drugs Under the conditions described the use of both dexamphetamine and phenmetrazine as well as inert tablets was associated with consistent loss of weight in the majority of patients It would have been interesting to have included a fourth period on the same diet during which no treatment with any form of drug was given, but this would have interfered with the " double-blind " nature of the trial, and for this reason it was omitted Both dexamphetamine and phenmetrazine were shown to be more effective than inert tablets, and in the doses used phenmetrazine was slightly more effective than dexamphetamine

14 of the patients originally accepted for the trial defaulted at various stages of the eighteen weeks of study (table V), but in no case was the trial discontinued because of side-effects or at the suggestion of the observers Up to the time that they defaulted, these patients were losing weight at a similar rate on each form of treatment to that of the patients who completed the trial For this reason the defaulters are unlikely to have affected the validity of the conclusions based on the results obtained from those who completed eighteen weeks of study

The remarkable reduction in the amount of weight lost by most of these patients in successive periods may not be due simply to weakening of resolve and failure to persist with the regimen A considerable loss of body-water (" initial dehydration ") is known to occur when obese patients start treatment with reducing diets This may be due to changing from a diet which includes a high intake of carbohydrate to a regimen on which the patient depends on endogenous fat for much of his energy requirements (Passmore, Strong, and Ritchie 1958) Such a mechanism could account for the striking difference in the mean loss of weight between the first and subsequent periods noted in table II

It is evident from fig 2 that after a period of twelve weeks the value of dexamphetamine and phenmetrazine in promoting loss of weight appears to be very limited, though in the period six to twelve weeks both compared favourably with the inert tablet

We may conclude that many obese patients will lose weight satisfactorily if suitably advised and provided they are seen regularly at short intervals Drugs of the type widely prescribed for the suppression of appetite have a limited place in the management of obesity, but they tend to be less effective when used for long periods

The problems raised by comparison of the cost of these drugs and the dangers of addiction cannot be ignored These have been discussed elsewhere by Duncan, Rose, and Meiklejohn (1960)

Summary

The value of dexamphetamine 5 mg b d and phenmetrazine 25 mg b d in promoting weight loss in obese patients has been compared with that of an inert tablet

Phenmetrazine appeared to be slightly more effective than dexamphetamine, but both were more effective than the inert tablet

Whatever the treatment used, loss of weight was greater during the first period of six weeks than in either of the two succeeding periods

Acknowledgments are due to colleagues who permitted us to study patients under their care We are particularly grateful to Miss A H Halley and her colleagues in the dietetic department for much help Dr F R Fletcher, of Messrs Pfizer Ltd, kindly arranged the preparation of the tablets used in the trial We are also indebted to Dr B Woolf, F R S E, of the Department of Animal Genetics, for his advice on the preparation of table IV

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THE DIURETIC ACTIVITY OF BENDROFLUAZIDE

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SINCE chlorothiazide was introduced by Novello and Sprague in 1957, the search for even more efficient oral diuretics of the benzothiadiazine group has advanced rapidly Hydrochlorothiazide (Fleming et al 1959) was soon followed by hydroflumethiazide (Blagg 1959, Edmonds and Wilson 1959, Kennedy et al 1959), and these preparations, which have a similar action to chlorothiazide, were shown to be about ten times more potent on a weight-for-weight basis

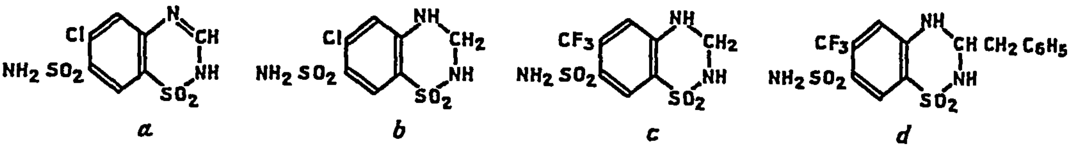

Fig 1—Chemical structure of (*a*) chlorothiazide, (*b*) hydrochlorothiazide, (*c*) hydroflumethiazide, and (*d*) bendrofluazide

Bendrofluazide ('Aprinox') is a further benzothiadiazine derivative which has still greater potency, weight for weight, than either hydrochlorothiazide or hydroflumethiazide The structural relations of chlorothiazide, hydrochlorothiazide, hydroflumethiazide, and bendrofluazide is shown in fig 1

We report here the results of volumetric and biochemical studies on nineteen œdematous patients and on two healthy male subjects, who received in all 59 doses of bendrofluazide Fourteen patients had congestive cardiac failure, three had hepatic cirrhosis, one had the nephrotic syndrome, and one woman had premenstrual œdema

Methods

The doses of bendrofluazide were 5 mg (5 times), 7 5 mg (50 times), or 10 mg (4 times)

Detailed biochemical and volumetric analyses were performed on the fourteen œdematous patients after a single dose of bendrofluazide (table I) Urine was collected for a control period of 24 hours before the drug was given (period I), and for two consecutive 12-hour periods thereafter (periods II and III), except in one patient (case 14) in whom a single 24-hour collection was made Blood samples were taken just before bendrofluazide was given, and again 24 hours later The urine collections were analysed in respect of volume, sodium, chloride, potassium, and inorganic-phosphorus content The urea, sodium, chloride, and potassium contents of the blood samples were determined

In a group of seven œdematous patients the serum-potassium level was determined before and after several doses of bendrofluazide (table II) Two of them were also submitted to detailed biochemical studies after a single dose

Two healthy young men were each given 5 mg, 7 5 mg, and 10 mg of bendrofluazide, with at least 7 days between each dose (table III) The urine was collected as before during periods I, II, and III, and the content of sodium, chloride,

TABLE I—BIOCHEMISTRY AND URINARY VOLUME STUDIES IN FOURTEEN PATIENTS BEFORE AND AFTER BENDROFLUAZIDE

Case no	Sex	Age (yrs)	Diagnosis	Dose (mg)	Period of study	Urine					Blood (plasma)
						(ml)	Volume (ml per hr)	Potassium (mEq per hr)	Sodium (mEq per hr)	Chloride (mEq per hr)	Potassium (mEq per litre)
1	M	35	Congestive cardiac failure	5 0	I	2270	94 6	2 98	9 72	8 85	4 4
			Rheumatic heart-disease		II	1505	125 3	3 51	12 91	13 87	
					III	1080	90 0	1 75	7 47	6 27	4 2
2	F	70	Congestive cardiac failure	5·0	I	1390	57 9	1 59	5 42	4 73	4 8
			Ischæmic heart-disease		II	980	81 7	1 88	9 33	9 07	
					III	950	79 3	1 67	7 95	6 95	4 7
3	F	45	Premenstrual œdema	5·0	I	1615	67 3	1 11	6 77	5 73	4 5
					II	2133	177 5	1 91	23 00	21 30	
					III	1250	104 2	1 41	12 14	9 63	4 1
4	M	35	Congestive cardiac failure	7·5	I	1480	61 6	1 91	6 47	4 24	4 3
			Rheumatic heart-disease		II	1745	145 3	4 07	23 40	21 68	
					III	450	37 5	0 96	4 36	4 40	4 2
5	M	59	Cirrhosis of liver	7 5	I	410	17 1	0 27	1 95	1 71	4 5
					II	1000	83 3	1 94	16 50	17 80	
					III	650	54 2	1 30	5 25	6 44	4 2
6	F	67	Congestive cardiac failure	7·5	I	1950	81 2	1 28	7 56	8 12	3 8
			Pernicious anæmia		II	2650	220 8	1 86	22·40	25 10	
					III	1965	163 7	1 27	17 58	16 23	3 8
7	F	64	Congestive cardiac failure	7 5	I	2110	87·9	1 72	6 16	6 12	4 5
			Rheumatic heart-disease		II	1230	102·5	1·43	11 83	10 05	
					III	1590	132·5	1·92	12 07	13 21	4 0
8	F	61	Congestive cardiac failure	7 5	I	1470	61 3	1 23	3 51	3 60	4 4
			Ischæmic heart-desease		II	1810	151·0	2·42	16 18	17 15	
					III	975	81 3	1 87	10 70	11 33	4·0
9	F	62	Cirrhosis of liver	7·5	I	770	29 6	1 19	3 21	2 34	4 6
					II	790	65 8	2 14	10 59	10 57	
					III	760	63 3	2·44	6 06	6 41	4 2
10	F	43	Congestive cardiac failure	7 5	I	1315	54 7	2 52	2 68	3 02	5 2
			Rheumatic heart-disease		II	1120	93 2	3 92	10·64	12 80	
					III	680	56 6	1 62	2 91	3 63	4 6
11	F	72	Congestive cardiac failure	7 5	I	595	24 8	0 63	1 38	0 56	3·6
			Thyrotoxicosis		II	457	38 0	1 29	6 40	5 68	
					III	1200	100·0	1 15	8 40	6 49	3 8
12	F	47	Cirrhosis of liver	7·5	I	2090	87 3	1 53	13 4	12 57	4 3
					II	2310	192 5	2·98	36 83	28 93	
					III	910	75 8	1 32	10 61	8 40	4 3
Mean values of above studies for 5 mg. dose					I	—	73 27	1 89	7 30	6 43	4 57
					II		128 17	2·63	15 08	14 75	
					III		90·50	1 61	9 19	8 45	4 33
„ „ „ „ „ „ 7 5 mg „					I		56·06	1 36	5 14	4 69	4 35
					II	—	121 32	2 45	17 19	16·64	
					III		84·98	1 54	8 66	8 50	4 12
Range (5 mg dose)					I		57·9–94·6	1 11–2·98	5 42–9 72	4 73–8 85	4 4–4 8
					II	—	81 7–177·5	1 88–3 51	9 33–23·00	9·07–21 30	
					III		79 3–104 2	1 41–1 76	7 47–12 14	6 27–9 63	4 1–4 7
„ (7 5 mg dose)					I		17 1–87·9	0 27–2·52	1·95–13 4	0 55–12 57	3·6–5 2
					II	—	38·0–220 8	1 43–4 07	6·4–36 83	5 69–28 93	
					III		37·5–163 7	0·96–2 44	2·91–17 58	3 63–16 23	3 8 4 6
13	M	55	Nephrotic syndrome	10	I	850	35·4	1·03	1·06	1 50	2·5*
					II	1200	100·0	2 38	7 35	7 40	
					III	1600	135·0	2 56	9 45	9 92	3·0
14	M	49	Congestive cardiac failure	10	I	910	37 9	1 39	1 43	1 26	4 4
			Rheumatic heart-disease Thyrotoxicosis		II III	1400	58 4	1 79	6 30	7 35	4 3

* Potassium chloride 6 g given by mouth in the following 24 hours

TABLE II—PLASMA-POTASSIUM LEVELS BEFORE AND AFTER SEVERAL DOSES OF BENDROFLUAZIDE IN SEVEN PATIENTS WITH CONGESTIVE CARDIAC FAILURE

Case no	Sex	Age (years)	Diagnosis	Dosage of bendrofluazide	Plasma-potassium (mEq per litre)		Comments
					Before	After	
6	F	67	Congestive cardiac failure Pernicious anæmia	5 doses of 7·5 mg in 11 days	3·75	4·6	Œdema disappeared, good hæmatological response to vitamin B_{12}
7	F	64	Congestive cardiac failure Rheumatic heart-disease	8 doses of 7·5 mg in 25 days	4·0	4·6	Œdema disappeared, digoxin also given
15	F	76	Congestive cardiac failure Pernicious anæmia	6 doses of 7·5 mg in 15 days	3·4	4·2	5 g potassium chloride given on 1st day of bendrofluazide therapy, digoxin also given, became free from œdema
16	F	34	Congestive cardiac failure Rheumatic heart-disease	7 doses of 7·5 mg in 18 days	4·6	4·7	Also given digoxin, became free from œdema
17	F	67	Congestive cardiac failure Myocardial infarction	5 doses of 7·5 mg in 9 days	4·7	4·6	Œdema disappeared, having anticoagulants but not digoxin
18	F	65	Congestive cardiac failure Ischæmic heart-disease	3 doses of 7·5 mg in 8 days	4·6	4·7	Digoxin also given, became free from œdema
19	F	42	Congestive cardiac failure Rheumatic heart-disease	5 doses of 7·5 mg in 12 days	5·5	4·8	Œdema disappeared, digoxin also given

potassium, inorganic phosphorus, and the volume, were estimated. A dose-response curve was plotted.

Flame photometry was used for the sodium and potassium estimations, silver-nitrate titration for chloride estimations (Wilson and Ball 1928), the method of Archer and Robb (1925) for urea estimations, and the method of Fiske and Subbarow (1925) for measuring inorganic phosphorus.

Results

The detailed volumetric and biochemical findings are given in the tables.

Diuresis and Dose of Bendrofluazide

With the 5 mg. dose of bendrofluazide a definite diuresis was obtained in all three œdematous patients (table I, cases 1–3) studied intensively (the mean volume in ml. per hour was period I, 73·27, II, 128·17, III, 90·50). One of the two normal subjects had a diuresis (table III).

A diuresis was obtained in all œdematous patients (table I, cases 4–12) who had the 7·5 mg. dose, and in the majority it was considerable (the mean volume in ml. per hour was period I, 56·06, II, 121·32, III, 84·98). A good diuresis was also obtained in the two normal subjects with a 7·5 mg. dose (the mean volume in ml. per hour was period I, 40·2, II, 136·3, III, 58·3).

TABLE III—URINARY VOLUME AND BIOCHEMISTRY IN TWO NORMAL SUBJECTS AFTER DIFFERING DOSES OF 5 MG., 7·5 MG., AND 10 MG. BENDROFLUAZIDE

Subject	Dose (mg.)	Period of study	Urine				
			Volume (ml.)	Volume (ml. per hr.)	Potassium (mEq per hr.)	Sodium (mEq per hr.)	Chloride (mEq per hr.)
Normal male, aged 25, body-weight 75·0 kg.	5	I	1675	69·8	4·64	9·78	10·57
		II	1035	86·1	4·96	17·07	23·4
		III	390	32·5	1·87	5·36	6·27
	7·5	I	990	41·2	3·55	7·84	7·22
		II	1650	140·0	4·75	31·68	31·90
		III	970	80·8	1·80	9·82	9·94
	10	I	1070	45·0	3·64	8·60	9·98
		II	1550	129·0	4·84	35·50	36·62
		III	1250	104·0	2·91	14·92	15·36
Normal male, aged 23, body-weight 74·1 kg.	5	I	1240	51·7	1·76	5·05	5·44
		II	1140	95·0	4·85	14·29	18·45
		III	900	75·0	1·60	8·47	6·76
	7·5	I	930	39·2	2·35	6·75	6·70
		II	1590	132·5	2·82	23·32	22·78
		III	430	35·8	1·43	6·18	6·22
	10	I	1160	48·4	1·86	5·75	5·74
		II	1720	143·2	2·65	21·70	24·15
		III	410	34·2	1·35	4·63	4·56
Mean values of above studies	5	I		60·75	3·20	7·42	8·00
		II		90·55	4·90	15·68	20·93
		III		53·75	1·73	6·92	6·52
	7·5	I		40·2	2·95	7·30	6·96
		II		136·3	3·78	27·50	27·34
		III		58·3	1·62	8·00	8·08
	10	I		46·7	2·75	7·18	7·86
		II		136·1	3·25	28·60	30·38
		III		70·4	2·13	9·78	9·96

In the two normal subjects the diuresis after the 10 mg. dose of bendrofluazide was not appreciably greater than with the 7·5 mg. dose (fig. 2). Likewise, the diuresis resulting from 10 mg. in two œdematous patients (table I, cases 13 and 14) was of the same order as that in the majority of œdematous patients who had 7·5 mg.

Time of diuresis.—In most of the patients studied the maximum diuresis was in the first 12 hours (period II) after bendrofluazide was given, while the diuresis was less, although still appreciable, in the second 12 hours (period III). In two patients (cases 7 and 11) with congestive cardiac failure, and in one (case 13) with the nephrotic syndrome, the diuresis was greater in the second 12 hours (period III).

Sodium and Chloride Excretion

Urinary sodium and chloride were both greatly increased after bendrofluazide. With the 5 mg. dose the mean increase in both sodium and chloride was about twofold (7·30–15·08 mEq per hour of sodium, and 6·43–14·75 mEq per hour of chloride). With the 7·5 mg. dose the mean sodium increase was more than threefold (5·14–17·19 mEq per hour), and the mean chloride increase was fourfold (4·69–16·64 mEq per hour). In the two normal subjects a 10 mg. dose did not significantly increase the sodium and chloride excretion over that of a 7·5 mg. dose (fig. 2). The times of maximum water diuresis and maximum excretion of sodium and chloride were closely related (fig. 3).

Potassium Excretion

Potassium excretion was increased, but to a lesser extent than that of sodium and chloride. The mean increase was about twofold with the 5 mg. dose (1·89–2·63 mEq per hour), and no further appreciable increase accompanied doses of 7·5 mg. or 10 mg. either in œdematous patients or normal subjects (table I, fig. 2).

Inorganic Phosphorus

The urinary excretion of phosphorus did not vary significantly in thirteen patients studied.

Blood Changes

The plasma levels of sodium, chloride, and urea before and after a single dose of bendrofluazide showed no significant change. The plasma-potassium level fell slightly (table I) in most of the patients studied after a single 7·5 mg. dose of bendrofluazide, and statistical analysis showed that the mean difference was significant at a 5% level ($t = 2·59$, with 8 degrees of freedom, $P < 0·05$).

In none of the seven œdematous patients who had several doses of bendrofluazide for periods of 8–25 days was the plasma-potassium level significantly altered

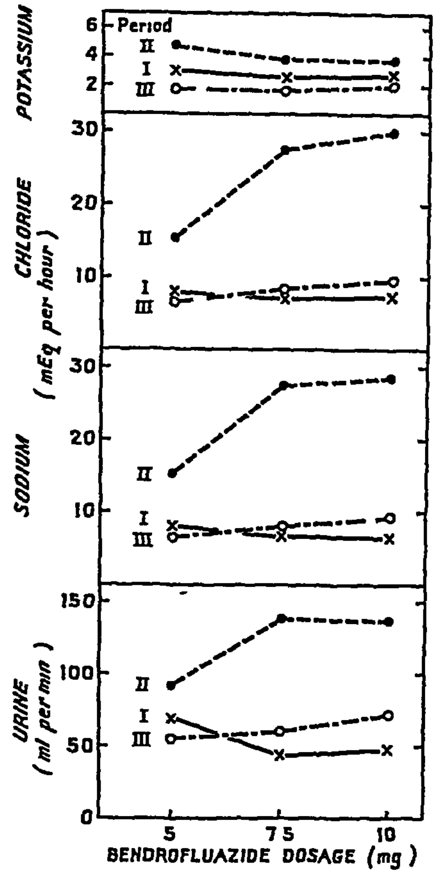

Fig 2—Effect of doses of 5 mg , 7 5 mg , and 10 mg of bendrofluazide on urine flow and electrolyte excretion (average of results in two normal subjects)

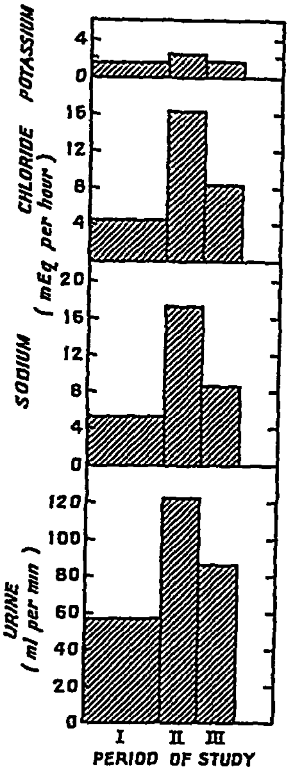

Fig 3—Urinary volume and electrolyte excretion 24 hours before (period I), 0-12 hours after (period II), and 12-24 hours after (period III) 7 5 mg bendrofluazide (mean values of 9 experiments)

(table II) One of these patients (case 15) was given a small potassium supplement (a total of 5 g potassium chloride) at the start of bendrofluazide treatment, no supplement was given to the others

Toxic Effects

No toxic effects were noted in any patient

Discussion

The trial undoubtedly shows that bendrofluazide is an effective oral diuretic in various conditions causing œdema Weight for weight it is much more potent than other benzothiadiazine derivatives so far described 7 5 mg of bendrofluazide seems to be as active as 2 g of chlorothiazide, 200 mg of hydrochlorothiazide, or 200 mg of hydroflumethiazide Our studies in the two normal subjects suggest that 7 5 mg is the optimum dose of bendrofluazide for people of average body-weight

The mode of action seems to be similar to that of other chlorothiazide derivatives—namely, an increased urinary excretion of sodium and chloride which causes a brisk osmotic diuresis Bendrofluazide acts mainly in the first 12 hours after administration, but in a few cases the action is rather more prolonged

Bendrofluazide, like other benzothiadiazine derivatives, causes an increased urinary excretion of potassium, but the loss is less than that of sodium and chloride In several of the patients studied the plasma-potassium level fell slightly 24 hours after bendrofluazide was given Probably this slight fall is often only temporary, because we observed no significant alteration in the plasma-potassium level in several patients with congestive cardiac failure, who had bendrofluazide twice or thrice weekly until they became free from œdema It seems, therefore, that the risk of hypokalæmia is not great, but, as with other benzothiadiazine derivatives (Kennedy 1960), it is probably desirable to give a potassium supplement if long-term therapy is required, or if the patient has hepatic cirrhosis

Summary

The biochemistry and urinary volume was studied in detail in fourteen œdematous patients before and after a single dose of bendrofluazide Similar studies were made in two healthy young men after increasing doses of bendrofluazide The plasma-potassium was determined before and after several doses of bendrofluazide in seven œdematous patients

Bendrofluazide is a powerful oral diuretic, acting by increasing the excretion of sodium and chloride, which causes osmotic diuresis The optimum dosage for most patients is probably 7 5 mg, but some will respond well to 5 mg, while a few may require 10 mg

The urinary excretion of potassium is increased by bendrofluazide, but less than is that of sodium and chloride The plasma-potassium level may fall slightly 24 hours after a single dose of bendrofluazide, but hypokalæmia was not observed in several patients with congestive cardiac failure who had the drug twice or thrice weekly for 8-25 days, with a satisfactory clinical effect

No toxic effects were noted

We wish to thank Prof L J Davis for encouragement throughout this study Bendrofluazide ('Aprinox') was supplied by Boots Pure Drug Co , Ltd

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INHIBITION OF CHOLESTEROL BIOSYNTHESIS BY FARNESOIC ACID AND ITS ANALOGUES

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According to one of the principal hypotheses concerning the pathogenesis of atherosclerosis, a high level of plasma-cholesterol is one of the initiating factors Cholesterol is continuously synthesised in the body (Schoenheimer 1946) as well as being supplied in the diet

3 acetyl-coenzyme A
↓
Acetoacetyl-coenzyme A + acetyl-coenzyme A
↓
3-hydroxy-3-methylglutaryl-coenzyme A
↓
Mevalonic acid
↓
5-phosphomevalonic acid
↓
5-diphosphomevalonic acid
↓
*Iso*pentenyl-pyrophosphate
↓
3,3-dimethylallyl-pyrophosphate
↓
Geranyl-pyrophosphate → geranic acid
↓
Farnesyl-pyrophosphate → farnesoic acid
↓
Squalene
↓
Lanosterol
↓
Cholesterol

Fig 1—Intermediates in biosynthesis of cholesterol.

of all but the strictest vegetarians, and it accumulates in the body whenever the supply (endogenous synthesis plus dietary content) is greater than elimination by degradation.

If excess of cholesterol is a cause factor in initiating human atherosclerosis—and there is as yet no proof of this —lowering the cholesterol content of the body might be a desirable preventive or therapeutic measure. From the known facts of cholesterol metabolism, one might attempt to decrease the cholesterol content of the body in three general ways (1) by inhibition of absorption from the intestine, (2) by stimulation of elimination, or (3) by inhibition of endogenous synthesis The experiments we report are related to the last possibility

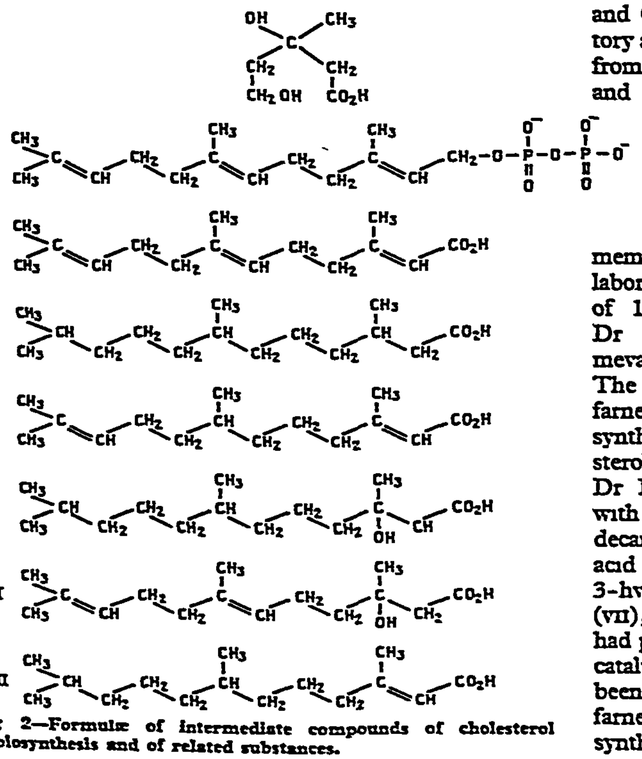

Fig 2—Formulæ of intermediate compounds of cholesterol biosynthesis and of related substances.

The biosynthesis of cholesterol is one of the most complex biological processes yet revealed The chain of reactions in its formation is summarised in fig 1

The early parts of this chain, preceding the formation of squalene, were elucidated after the discovery of mevalonic acid (fig 2 I) in 1956 (for review see Popják and Cornforth 1960) by research-workers at the Merck Sharp & Dohme Research Laboratories, New Jersey, U S.A. (see Folkers et al 1959)

Theoretically one could inhibit cholesterol synthesis by interfering with any one reaction in the long synthetic chain But it seems undesirable to interfere with the reactions preceding the formation of mevalonic acid, since acetyl-coenzyme A, acetoacetyl-coenzyme A, and 3-hydroxy-3-methylglutaryl-coenzyme A are also involved in metabolic reactions other than the synthesis of cholesterol Beyond the stage of mevalonic acid, on the other hand, interference would cause more specific inhibition of sterol biosynthesis, for the only metabolic process, other than the biosynthesis of sterol, in which mevalonic acid is known to be involved in animals is the synthesis of the side-chain of ubiquinone—i e., coenzyme Q (Gloor and Wiss 1958, Dialameh and Olson 1959)

During investigation of the biosynthesis of cholesterol in liver-enzyme preparations, some of the intermediates —but mainly farnesyl pyrophosphate (fig 2 II)—were found to be metabolised by liver enzymes on an alternative pathway to carboxylic acids—e.g , to farnesoic (*trans*-*trans*-3,7,11-trimethyldodeca-2,6,10-trienoic) acid (fig 2 III), Popják Horning, Bucher, and Cornforth 1959, Popják 1959) These carboxylic acids, of which farnesoic acid is only one, are not intermediates in cholesterol biosynthesis On the contrary, they represent part of a pathway for the catabolic disposal of intermediates, like farnesyl pyrophosphate, and they also inhibit the utilisation of intermediates of cholesterol synthesis, hence they may be part of a physiological controlling mechanism Although Dituri et al. (1957) reported that farnesoic acid was incorporated into cholesterol, this could not be confirmed in our laboratory (N L R. Bucher, M Horning, and G Popják, unpublished observations) The inhibitory action of farnesoic acid on the synthesis of cholesterol from mevalonate in vitro was first described by Wright and Cleland (1957), and we readily confirmed this observation. It was then a logical step to test analogues of farnesoic acid for their effect on cholesterol synthesis, in the hope that some might prove more powerful inhibitors than farnesoic acid itself

One of us (G P) discussed these problems with members of the Merck Sharp & Dohme research laboratories during a visit to New Jersey in the summer of 1958 The Merck organisation group included Dr Karl Folkers' research team, which discovered mevalonic acid, a key intermediate in sterol biosynthesis The Merck group were already working on analogues of farnesoic acid as possible inhibitors of cholesterol synthesis, although the exact relation of farnesoic acid to sterol biosynthesis was not known at that time Later Dr Folkers, Dr Sprague, and Dr Bolhofer provided us with five substances (see fig 2) 3,7,11-trimethyldodecanoic acid (IV), 3,7,11-trimethyldodeca-2,10-dienoic acid (V), 3-hydroxy-3,7,11-trimethyldodecanoic acid (VI), 3-hydroxy-3,7,11-trimethyldodeca-6,10-dienoic acid (VII), and 3,7,11-trimethyldodec-2-enoic acid (VIII) We had previously made the first of these compounds (IV) by catalytic hydrogenation of farnesoic acid and this has been described in detail, together with the synthesis of farnesoic acid (Popják and Cornforth 1960) The chemical synthesis and characterisation of the compounds sent to

Results

The 25 positive cases (table I) fall into three groups

Group 1 includes 3 women, from whom listeria were isolated in the second trimester of their pregnancy and who aborted shortly afterwards In case 1 listeria were isolated from the amniotic fluid of the aborted pregnancy

Group 2 comprises 8 women from whom listeria were isolated during the first trimester of pregnancy (case 4 during the second trimester) They received treatment and their pregnancies proceed regularly

Group 3 comprises 14 women from whom listeria microorganisms were isolated when non-pregnant

All these women had 1 to 6 abortions in periods of time up to eight years The period during which they were positive to listeria, from the first positive culture until cultures became negative after treatment, was up to twenty weeks

None of the positive women had any complaints, with the exception of case 2 (group 3), who suffered from vaginal discharge and itching It is worth mentioning that listeria could be isolated in this case only after trichomonas infection was cleared

In 3 of the 9 negative cases (table II) abortions could be attributed to other causes Most of these patients were examined at the beginning of the investigation, and they are being studied again by our standard method

None of the 87 control women harboured listeria in their genital organs

The following case (case 5, group 3) deserves special mention

A 24-year-old had a history of (1) stillbirth at 7th month, (2) missed abortion at 6th month, (3) stillbirth at 7th month, (4) missed abortion at 5th month, all in the course of 5 years She was referred to us for investigation eight months after her last abortion and *Listeria monocytogenes* was isolated from her cervical secretion She disappeared and came back four months later with a missed abortion The ovum was expelled whole and listeria were cultivated from the liquor amnii The macerated fœtus was 13 cm long

The earliest fœtus reported in the literature from which listeria microorganisms were isolated was described by Stark (1953) it was 25 cm long, in the fifth month of pregnancy

TABLE II—REPEATED ABORTION NEGATIVE TO LISTERIA

No	Age (yr)	No of pregnancies preceding examination	No of live births exc neonatal deaths	No of abortions (and stillbirths or neonatal deaths)	No of negative cultures	Observations
1	24	2		1 (1)	1	
2	24	6		3 (2)	4	1 artificial abortion. Incompetence of internal os
3	23	7		7	5	Very early abortions The husband has oligospermia, hypokinesis
4	27	5	1	4	3	
5	34	5	1	4	2	Very early abortions The husband has oligospermia, hypokinesis
6	30	4		2 (2)	1	
7	28	5	3	2	3	
8	36	3		1 (2)	1	
9	35	4	1	2 (1)	3	

Seeliger (1957), a leading authority on listeriosis, writes "Unfortunately, bacteriology does not give us the answer in all cases, particularly in those cases where the diagnosis is suspected but Listeria cannot be cultivated Up to now, no one has succeeded in isolating *Listeria monocytogenes* from pregnant women before the *disease is manifest in the newborn* —" He still holds this opinion

Treatment

All the pregnant women in group 2 (table I) are now under treatment Treatment was started immediately the infection was proved 11 out of 14 non-pregnant women of group 3 are under treatment as well, to enable them to become pregnant without undue risk of abortion.

Treatment generally consisted of large doses of penicillin (1 million units daily for fourteen days) and sulphamethoxypyridazine ('Lederkyn') 1 g daily for fourteen days In most cases the cervical cultures became negative after five or six days As we found that cultures became positive again one to six weeks after stopping treatment, we believe that maintenance doses of sulphamethoxypyridazine (0 5 g daily) should be continued for long

TABLE I—REPEATED ABORTION DUE TO GENITAL LISTERIOSIS

—	Case	Age (yr)	No of pregnancies preceding diagnosis	No of live births exc. neonatal deaths	No of abortions (and stillbirths or neonatal deaths)	Month of pregnancy when listeria diagnosed	No of positive cultures	Duration of positivity (weeks)	Presumed minimal duration of infection	Observations
Group 1	1	22	3		2 (1)	6th	1		3 yr	Listeria isolated from cervix. 5 days later aborted. Listeria isolated from amniotic fluid After abortion, cervical secretion negative for 2 months
	2	33	6	1	4 (1)	6th	1		?	Aborted in the 6th month Then negative for 2 weeks
	3	25	1		1	4th	1		3½ yr	Aborted in the 4th month. Then negative during 3 weeks Again positive after 1 month
Group 2	1	32	8	2	1 (3)	2nd	5	18	14 yr	Now pregnant 7th mo 2 artificial abortions
	2	22	2		1 (1)	2nd	4	10	2 yr	,, ,, 6th ,,
	3	35	8	5	3	3rd	4	10	1½ yr	,, ,, 6th ,,
	4	32	5	1	4	5th	2	1	8 yr	,, ,, 5th ,,
	5	26	3		3	3rd	2	1	2½ yr	,, ,, 5th ,,
	6	41	5	2	3	2nd	5	5	5 yr	,, ,, 4th ,,
	7	30	3	1	2	2nd	2	1	3 yr	,, ,, 3rd ,,
	8	33	4		4	1st	2	1	6 yr	,, ,, 3rd ,,
Group 3	1	37	5	2	2 (1)		12	18	2 yr	
	2	32	3	1	2		11	18	2½ yr	
	3	23	2		2		15	20	2 yr	
	4	25	6	3	2		6	20	1½ yr	1 artificial abortion
	5	24	5		3 (2)		1		5 yr	Positive before last pregnancy, then aborted at 4th month *Listeria* isolated from amniotic fluid
	6	34	6		4		4	8	5 yr	
	7	33	7	1	6		7	14	8 yr	
	8	25	1		1		4	10	4 mos	
	9	26	4	1	2		4	6	16 mos	1 artificial abortion
	10	22	3	1	2		4	7	1 yr	
	11	27	3	1	2		3	1	1½ yr	
	12	23	2		2		3	3	9 mos	
	13	27	2		2		3	1	7 mos	
	14	30	4		3		3	1	2 yr	1 artificial abortion

periods This is our policy at present Our short experience with treatment does not allow us to say more It is noteworthy that all the pregnant patients under treatment are well and their pregnancies are proceeding normally

Summary

A relationship between listeria microorganisms and repeated abortion has been proved Listeria were isolated from the genital organs of 25 out of 34 women with a history of repeated abortion Listeria microorganisms were also isolated from aborted products of conception

Genital listeriosis has been described as a state of chronic listeria infection of the genital organs of apparently healthy women Genital listeriosis manifests itself by the continuous excretion of organisms from the uterine cervix over long periods and by abortion or premature stillbirth in supervening pregnancies

Pregnant women affected by genital listeriosis have not so far aborted after treatment with penicillin and sulphamethoxypyridazine

We are indebted to Dr H P R. Seeliger, of the Institute of Hygiene, University of Bonn, Germany, for his identification of cultures We wish to thank Prof Joseph Asherman for referring to us many of his patients for diagnosis and treatment We are grateful to the American Cyanamid Co , Lederle Laboratories Division, for the supply of ' Lederkyn ' for this investigation

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EPIDEMIC CERVICAL MYALGIA

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ACUTE cervical myalgia " stiff neck " is fairly common, and its true incidence is probably even greater than is generally appreciated, because many sufferers do not trouble their doctors with symptoms that are familiar and usually short-lived

The ætiology is unknown Patients usually attribute their symptoms to the effects of draughts, while their doctors often invoke that ill-defined condition—" fibrositis "—to explain the illness Infection does not seem to have been suggested as a cause until Massell and Solomon (1935) and, later, Beeson and Scott (1941, 1942) concluded, from retrospective surveys based on questionaries answered by patients, that acute " stiff neck " could occur in epidemic form Subsequently, other outbreaks of acute myalgia, principally affecting the trapezius muscles, were described by Copeman (1944) and Wilson (1946) All these workers agreed that epidemic " stiff neck " was probably an infection, possibly due to a virus, and that clinically the condition was distinct from Bornholm disease Beeson and Scott (1941, 1942) tried to transmit the disease to volunteers, using throat washings and/or blood taken from affected patients Throat washings had no apparent effect, but inoculation with blood appeared to produce the disease in some volunteers, though the evidence was not conclusive Attempts to infect laboratory animals and developing chick embryos failed

Present Investigation

In the autumn of 1958 and again in the late summer of 1959 a small epidemic of acute myalgia, principally affecting the trapezius muscles, occurred among nurses at this hospital In all, 13 nurses reported sick—7 in the first epidemic and 6 in the second The total nursing staff at the main hospital numbers about 725, so the attack-rate seems very small Inquiries among the nurses suggests, however, that many others were affected during the relevant periods but did not consider their symptoms severe enough to seek medical advice

All except 1 of the 13 nurses who reported sick were admitted, and the condition was studied more fully than appears to have been possible before

CASE-RECORDS

Case 1 —A 21-year-old nurse was admitted on Aug 7, 1958 For a day she had had severe pain in the neck which began suddenly and was aggravated by movement She was in considerable pain and held her neck flexed to the right Though there was no true neck stiffness, all movements were restricted by pain Both trapezius muscles were extremely tender to palpation over most of their extent, but there were no other abnormal physical signs and she was afebrile

Progress —After admission there was slight intermittent pyrexia, of up to 99 6° F, for four days The pain in her neck gradually abated, but six days after admission aching pain developed in both hands and both knees unaccompanied by stiffness or swelling These symptoms disappeared within twenty-four hours, and thereafter she was quite well

Case 4 —A 20-year-old nurse was admitted on Sept 8, 1958 That morning she had suddenly experienced very severe interscapular pain spreading to both scapular regions, aggravated by movement and breathing She was in severe pain Though there was no true neck stiffness all movements were restricted by pain, and both trapezius muscles were very tender to palpation There were no other abnormal physical signs and she was afebrile

Progress —The pain in the neck remained severe for nine days, after which it gradually subsided Seven days after admission the patient complained of pain in both knees and both ankles which lasted for four days, there was no associated swelling or restriction of movement The patient remained in hospital for twelve days, and from the fourth day until discharge there was intermittent pyrexia of up to 100°F On discharge she was symptom-free

Case 9 —A 20-year-old nurse was admitted on Aug 3, 1959 For one day she had had vague abdominal aching and nausea On the day of admission aching developed in the neck, lower back, and legs She was afebrile There was severe tenderness of both trapezius muscles, but no other abnormal physical signs

Progress —A few hours after admission the patient's temperature rose to 101°F, but later on the same day it fell to normal again and remained so until the sixth day when it rose to 99°F She was discharged on sick leave, apparently cured, eight days after admission, but the following day she was readmitted because of generalised muscular aches headache, and neck stiffness which had made her family doctor suspect poliomyelitis Lumbar puncture was now carried out, but the cerebrospinal fluid was normal in all respects After a further nine days, during which she complained of transient fleeting muscular pains, she recovered completely Throughout the second admission she was afebrile us by Dr Folkers will be reported shortly The chemical relation of compounds IV–VIII to farnesoic acid is evident from their formulæ All these acids were tested for their ability to inhibit the biosynthesis of cholesterol from mevalonate in liver-enzyme preparations

Methods

Homogenates of rat liver were prepared as described by Bucher and McGarrahan (1956) in 0 1 M potassium-hydrogen-phosphate buffer, pH 7 4 containing 0 005 M $MgCl_2$ and 0 03 M nicotinamide The homogenates were centrifuged at 10,000 *g* for 25 minutes to sediment the unbroken cells, nuclei, and mitochondria The supernatants (S_{10} preparations) of the centrifuged homogenates, which were shown to synthesise cholesterol from mevalonic acid, were used as previously described (Popják et al 1958) For each test 5 ml incubations were set up containing 4 ml of S_{10}, to which was added 2 µmoles each of reduced diphosphopyridine nucleotide and triphosphopyridine nucleotide, 5 µmoles of adenosine triphosphate (A T P), and 2 µmoles of DL−[2−^{14}C] mevalonate The test substances, as potassium salts, were added to the incubations in concentrations of $0\ 2 \times 10^{-3}$ M to 2×10^{-3} M The reaction mixtures were incubated aerobically at 37°C for 2 hours, after which they were hydrolysed with 2N KOH The unsaponifiable substances were extracted with light petroleum and cholesterol (and other 3β-hydroxysterols) precipitated as the digitonide and prepared for radioactive counting as described by Popják et al (1958) From the known specific activity of the [2−^{14}C] mevalonate (0 2 µC per µmole), and from the radioactivity of the isolated sterol-digitonides, could be calculated the number of *micromoles of mevalonate converted into sterol* Two types of control were used one contained only the components of the enzyme system with its coenzymes, the other contained potassium dodecanoate (laurate) to guard against the possibility that the effect of the various substances was only that of a soap

In addition to this complete enzyme system we also tested the effects of compounds IV–VII and of farnesol on purified liver mevalonic kinase In experiments with this enzyme we used the standard spectrophotometric assay described by Levy and Popják (1959, 1960) for liver mevalonic kinase This assay measures the rate of phosphorylation of mevalonic acid (µmoles per min per mg protein) The enzyme preparation which we used phosphorylated 1 2 µmoles of mevalonate per min per mg protein at 37°C in the absence of an inhibitor In our experiments the rate of phosphorylation of mevalonate in the presence of an inhibitor was compared with the rate observed in the control

TABLE I—INHIBITION OF CHOLESTEROL BIOSYNTHESIS IN VITRO BY FARNESOIC ACID AND ITS ANALOGUES

All experiments were made under identical conditions (see text) except that a different enzyme preparation was used in each

Experiment no	Substance added, with concentration (m/molar)	Mevalonate converted into cholesterol (µmoles)	% inhibition
1	None, control	0 370	0
	IV 0 2	0 240	35
	IV 0 4	0 170	54
	IV 1 0	0 002	>99
	IV 2 0	0 000	100
	V 0 2	0 380	0
	V 0 4	0 082	78
	V 1 0	0 000	100
	V 2 0	0·000	100
2	None, control	0 630	0
	Potassium laurate, 1 0	0 640	0
	VI 0 2	0·480	24
	VI 0 4	0 055	91
	VI 1·0	0·000	100
	VII 0 2	0 305	52
	VII 0 4	0·098	85
	VII 1·0	0 000	100
3*	None, control	0·408	
	VIII 0 2	0·607	
	VIII 0 4	0 577	
	VIII 1·0	0 496	
	Potassium laurate, 0·4	0 557	
	1·0	0 563	
4	None, control	0 509	
	None, control	0·525	
	IV 0 2	0 310	40
	IV 0 4	0·044	91
	IV 1 0	0 000	100
	III 0 2	0·437	16
	III 0·4	0 375	28
	III 1 0	0 357	31

* This experiment was repeated with identical results

TABLE II—EFFECTS OF ANALOGUES OF FARNESOIC ACID ON PURIFIED LIVER MEVALONIC KINASE

The test system was the standard spectrophotometric assay (Levy and Popják 1959, 1960) for liver mevalonic kinase The enzyme used phosphorylated, in the absence of an inhibitor, 1 2 µmoles of mevalonate per min per mg protein All substances tested were added in 1 millimolar (=1 µmole per ml) final concentration

Substance	*% inhibition*
IV	94 8
V	40 7
VI	76 5
VII	31 0
Farnesol	0

In the spectrophotometric assay of mevalonic kinase the formation of adenosine diphosphate (A D P) from A T P during phosphorylation of mevalonate is measured with the aid of pyruvic kinase and lactic dehydrogenase according to the following reactions (1), (2), and (3)

$$1\quad \text{Mevalonate} + \text{A T P} \xrightarrow{\text{mevalonic kinase}} \text{5-phosphomevalonate} + \text{A D P}$$

$$2\quad \text{A D P} + \text{phosphoenolpyruvate} \xrightarrow{\text{pyruvic kinase}} \text{pyruvic acid} + \text{A T P}$$

$$3\quad \text{Pyruvic acid} + \text{D P N H} \xrightarrow{\text{lactic dehydrogenase}} \text{lactic acid} + \text{D P N}$$

We ascertained that the substances tested had no effect on reactions (2) and (3)

Results and Discussion

Our results (table I) showed that all the substances tested, except compound VIII and potassium laurate, inhibited cholesterol synthesis very strongly The action of farnesoate compared with that of its analogues (IV–VII) was feeble, substantial inhibitions (80–90%) could be achieved with farnesoate only at higher concentrations ($10 \times 10^{-3}M$) The fact that compound VIII and potassium dodecanoate had no inhibitory action, and even stimulated slightly the conversion of mevalonate into cholesterol, suggests that the effect of the other substances is specific

The mechanism of action of compounds IV–VII is not known in detail So far we have investigated their effect on only one of the enzymes—mevalonic kinase—involved in the chain of biosynthesis (see fig 1) Mevalonic kinase (Tchen 1958, Levy and Popják 1959, 1960) is the enzyme responsible for the first transformation of mevalonic acid, the product of its action being 5-phosphomevalonate It has already been reported (Levy and Popják 1960) that compound IV strongly inhibited mevalonic kinase. Further tests made in collaboration with Dr Levy showed that compounds V, VI, and VII also inhibited mevalonic kinase, but not as strongly as did compound IV The results of the experiments with purified mevalonic kinase are summarised in table II Only compound IV showed powers of inhibiting mevalonic kinase comparable to those found in the complete cholesterol-synthesising system This suggests that compounds V, VI, and VII act also on reactions of the synthetic chain beyond that catalysed by mevalonic kinase

The results of the experiments with the analogues of farnesoic acid in vitro, encouraged us to test them also in vivo, but as yet we have no information about their effects in animals

Summary

Analogues of farnesoic acid (*trans-trans*-3,7,11-trimethyldodeca-2,6,10-trienoic acid) were tested for their effects on the biosynthesis of cholesterol from mevalonate in liver-enzyme preparations

Four substances—3,7,11-trimethyldodecanoate, 3 7,11-trimethyldodeca-2,10-dienoate, 3-hydroxy-3,7,11-trimethyldodecanoate, and 3-hydroxy-3,7,11-trimethyldodeca-6,10-dienoate—in concentrations of 1 m*M* (1 μmole per ml) abolished completely the synthesis of cholesterol from mevalonate A fifth substance—3,7,11-trimethyldodec-2-enoate—had no inhibitory action. The active substances were far more potent inhibitors than was farnesoic acid

The effect of 3,7,11-trimethyldodecanoate may be attributed almost entirely to its inhibition of mevalonic kinase. Although the other three inhibitors affected mevalonic kinase, they probably also act on reactions catalysed by other enzymes in the biosynthetic chain of cholesterol.

Testing the inhibitors of cholesterol biosynthesis in vivo seems to be justified because they may lower body cholesterol levels by decreasing endogenous synthesis

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GENITAL LISTERIOSIS AS A CAUSE OF REPEATED ABORTION

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Repeated abortion is seldom satisfactorily explained, and the distressing inability to offer any real help in these cases prompted us to seek a new approach We found that a hitherto unknown form of human listeriosis—genital listeriosis—is an important cause of abortion and repeated abortion. By genital listeriosis we mean a state of chronic infection of the genital organs of apparently healthy women by listeria microorganisms It manifests itself by the continuous excretion of microorganisms from the uterine cervix over long periods, and by abortion or premature stillbirth in supervening pregnancies

Microorganisms belonging to the genus listeria were first isolated from animals by Murray et al (1926) and by Pirie (1927) Nyfeldt (1929) was the first to isolate listeria from a human case Murray (1955) stated that microorganisms belonging to the genus listeria were isolated from 27 species of animals in 26 countries all over the globe, among them Israel Their pathogenicity for humans has been proved beyond doubt, for listeria microorganisms have been isolated from a variety of diseases such as meningitis, infectious mononucleosis, pneumonia endocarditis, granulomatosis infantiseptica (Potel 1951, 1952) &c

It is known (Murray et al 1926, Gray 1958, Schultz 1957, Suchanova et al 1958, Young and Firehammer 1958, Gray et al 1955) that listeriosis causes abortion in wild and domestic animals. so in the case of a 37-year-old woman with a history of three consecutive unexplained abortions over a period of two years, we looked for listeria organisms We cultured swabs from cervical and vaginal secretions and the cultures were repeatedly positive (twelve times in four months) In fact listeriosis has been lately suspected to cause habitual abortion in the human (Seeliger and Cherry 1957, Rost et al. 1958), but this opinion has either not been accepted (Potel and Alex 1956) or flatly rejected.

Reviews by Gray et al (1957), Seeliger and Cherry (1957), Krepler and Flamm (1956), and Hoeprich (1958) record considerable progress in the investigation of the bacteriological, serological, and clinical aspects of listeriosis Nevertheless, it is apparent that research in this rapidly expanding subject is still at its beginning The main cause of this lag is the great difficulty encountered in primary isolation of listeria from pathological material

Following our first success, investigation was conducted in two directions

(1) The development of a simple and rapid method for the primary culturing of these microorganisms

(2) A search for listeria in a large series of cases of repeated abortions

Material and Methods

Material for cultures was obtained from the cervical secretion with sterile swabs The swabs were kept in the refrigerator until cultured. The culture medium was prepared as follows

The following ingredients were dissolved in 1000 ml of distilled water and autoclaved for fifteen minutes at 15 lb pressure

Bacto tryptose	20 g
Bacto beef extract	3 g
Sodium chloride	5 g
Dextrose	1 g
Bacto agar	20 g

Just before pouring the plates, 1 ml of 0·5% sterile solution of vitamin B_1 (aneurine HCl *B.P*) in distilled water was added The final pH was 6 7–6 8

The plates were incubated at 37 C for twenty-four hours to test for sterility, then they were directly streaked from the swabs rich in cervical secretion, and incubated in candle jars at 37 C for twenty-four hours The agar plates were then examined for the characteristic type of growth—e g , small round colonies (Gray et al 1957) Microscopic smears from these colonies were considered positive on finding typical gram-positive rods as described by Gray et al. (1957) The strains from all cases were kept in stab cultures for further investigation and storage Some of these strains were sent to Dr H P R Seeliger in Bonn, Germany, for typing The strains that arrived alive were typed *Listeria monocytogenes* 4b (Seeliger 1959)

Within a period of five months we examined 34 women with a history of repeated abortion. Of these, 25 were positive, i e , listeria microorganisms were isolated at least three times from material taken at one to five days' intervals Pregnant women with two positive cultures at one-day interval were considered positive, since treatment had to be started immediately for obvious reasons

87 controls (women of reproductive age, married or unmarried, healthy or affected by irrelevant gynæcological conditions, such as dysmenorrhœa, amenorrhœa, [illegible]ital prolapse, stress incontinence, &c.), were [illegible]med None of the controls had a history of abortions

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* Professor Rappaport died on July 17, 1959, and his coauthors acknowledge his invaluable cooperation, which was interrupted by his illness He was not responsible for the final conclusions reached in this paper

Results

The 25 positive cases (table I) fall into three groups

Group 1 includes 3 women, from whom listeria were isolated in the second trimester of their pregnancy and who aborted shortly afterwards In case 1 listeria were isolated from the amniotic fluid of the aborted pregnancy

Group 2 comprises 8 women from whom listeria were isolated during the first trimester of pregnancy (case 4 during the second trimester) They received treatment and their pregnancies proceed regularly

Group 3 comprises 14 women from whom listeria microorganisms were isolated when non-pregnant

All these women had 1 to 6 abortions in periods of time up to eight years The period during which they were positive to listeria, from the first positive culture until cultures became negative after treatment, was up to twenty weeks

None of the positive women had any complaints, with the exception of case 2 (group 3), who suffered from vaginal discharge and itching It is worth mentioning that listeria could be isolated in this case only after trichomonas infection was cleared

In 3 of the 9 negative cases (table II) abortions could be attributed to other causes Most of these patients were examined at the beginning of the investigation, and they are being studied again by our standard method

None of the 87 control women harboured listeria in their genital organs

The following case (case 5, group 3) deserves special mention

A 24-year-old had a history of (1) stillbirth at 7th month, (2) missed abortion at 6th month, (3) stillbirth at 7th month, (4) missed abortion at 5th month, all in the course of 5 years She was referred to us for investigation eight months after her last abortion and *Listeria monocytogenes* was isolated from her cervical secretion She disappeared and came back four months later with a missed abortion The ovum was expelled whole and listeria were cultivated from the liquor amnii The macerated fœtus was 13 cm long

The earliest fœtus reported in the literature from which listeria microorganisms were isolated was described by Stark (1953) it was 25 cm long, in the fifth month of pregnancy

Seeliger (1957), a leading authority on listeriosis, writes "Unfortunately, bacteriology does not give us the answer in all cases, particularly in those cases where the diagnosis is suspected but Listeria cannot be cultivated Up to now, no one has succeeded in isolating *Listeria monocytogenes* from pregnant women before the disease is manifest in the newborn —" He still holds this opinion

TABLE II—REPEATED ABORTION NEGATIVE TO LISTERIA

No	Age (yr)	No of pregnancies preceding examination	No of live births exc. neonatal deaths	No of abortions (and stillbirths or neonatal deaths)	No of negative cultures	Observations
1	24	2		1 (1)	1	
2	24	6		3 (2)	4	1 artificial abortion. Incompetence of internal os
3	23	7		7	5	Very early abortions The husband has oligospermia, hypokinesis
4	27	5	1	4	3	
5	34	5	1	4	2	Very early abortions The husband has oligospermia, hypokinesis
6	30	4		2 (2)	1	
7	28	5	3	2	3	
8	36	3		1 (2)	1	
9	35	4	1	2 (1)	3	

Treatment

All the pregnant women in group 2 (table I) are now under treatment Treatment was started immediately the infection was proved 11 out of 14 non-pregnant women of group 3 are under treatment as well, to enable them to become pregnant without undue risk of abortion.

Treatment generally consisted of large doses of penicillin (1 million units daily for fourteen days) and sulphamethoxypyridazine ('Lederkyn') 1 g daily for fourteen days In most cases the cervical cultures became negative after five or six days As we found that cultures became positive again one to six weeks after stopping treatment, we believe that maintenance doses of sulphamethoxypyridazine (0 5 g daily) should be continued for long

TABLE I—REPEATED ABORTION DUE TO GENITAL LISTERIOSIS

—	Case	Age (yr)	No of pregnancies preceding diagnosis	No of live births exc neonatal deaths	No of abortions (and stillbirths or neonatal deaths)	Month of pregnancy when listeria diagnosed	No of positive cultures	Duration of positivity (weeks)	Presumed minimal duration of infection	Observations
Group 1	1	22	3		2 (1)	6th	1		3 yr	Listeria isolated from cervix 5 days later aborted Listeria isolated from amniotic fluid After abortion, cervical secretion negative for 2 months
	2	33	6	1	4 (1)	6th	1		?	Aborted in the 6th month Then negative for 2 weeks
	3	25	1		1	4th	1		3½ yr	Aborted in the 4th month Then negative during 3 weeks Again positive after 1 month
Group 2	1	32	8	2	1 (3)	2nd	5	18	14 yr	Now pregnant 7th mo 2 artificial abortions.
	2	22	2		1 (1)	2nd	4	10	2 yr	,, ,, 6th ,,
	3	35	8	5	3	3rd	4	10	1½ yr	,, ,, 6th ,,
	4	32	5	1	4	5th	2	1	8 yr	,, ,, 5th ,,
	5	26	3		3	3rd	2	1	2½ yr	,, ,, 5th ,,
	6	41	5	2	3	2nd	5	5	5 yr	,, ,, 4th ,,
	7	30	3	1	2	2nd	2	1	3 yr	,, ,, 3rd ,,
	8	33	4		4	1st	2	1	6 yr	,, ,, 3rd ,,
Group 3	1	37	5	2	2 (1)		12	18	2 yr	
	2	32	3	1	2		11	18	2½ yr	
	3	23	2		2		15	20	2 yr	
	4	25	6	3	2		6	20	1½ yr	1 artificial abortion
	5	24	5		3 (2)		1		5 yr	Positive before last pregnancy, then aborted at 4th month. Listeria isolated from amniotic fluid
	6	34	6		4		4	8	5 yr	
	7	33	7	1	6		7	14	8 yr	
	8	25	1		1		4	10	4 mos	
	9	26	4	1	2		4	6	16 mos	1 artificial abortion
	10	22	3	1	2		4	7	1 yr	
	11	27	3	1	2		3	1	1½ yr	
	12	23	2		2		3	3	9 mos	
	13	27	2		2		3	1	7 mos	
	14	30	4		3		3	1	2 yr	1 artificial abortion

periods This is our policy at present. Our short experience with treatment does not allow us to say more. It is noteworthy that all the pregnant patients under treatment are well and their pregnancies are proceeding normally

Summary

A relationship between listeria microorganisms and repeated abortion has been proved. Listeria were isolated from the genital organs of 25 out of 34 women with a history of repeated abortion. Listeria microorganisms were also isolated from aborted products of conception.

Genital listeriosis has been described as a state of chronic listeria infection of the genital organs of apparently healthy women. Genital listeriosis manifests itself by the continuous excretion of organisms from the uterine cervix over long periods and by abortion or premature stillbirth in supervening pregnancies

Pregnant women affected by genital listeriosis have not so far aborted after treatment with penicillin and sulphamethoxypyridazine

We are indebted to Dr H. P R. Seeliger, of the Institute of Hygiene, University of Bonn, Germany, for his identification of cultures. We wish to thank Prof Joseph Asherman for referring to us many of his patients for diagnosis and treatment We are grateful to the American Cyanamid Co , Lederle Laboratories Division, for the supply of 'Lederkyn' for this investigation.

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EPIDEMIC CERVICAL MYALGIA

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Acute cervical myalgia "stiff neck" is fairly common, and its true incidence is probably even greater than is generally appreciated, because many sufferers do not trouble their doctors with symptoms that are familiar and usually short-lived.

The ætiology is unknown. Patients usually attribute their symptoms to the effects of draughts, while their doctors often invoke that ill-defined condition—"fibrositis"—to explain the illness Infection does not seem to have been suggested as a cause until Massell and Solomon (1935) and, later, Beeson and Scott (1941, 1942) concluded, from retrospective surveys based on questionaries answered by patients, that acute "stiff neck" could occur in epidemic form Subsequently, other outbreaks of acute myalgia, principally affecting the trapezius muscles, were described by Copeman (1944) and Wilson (1946) All these workers agreed that epidemic "stiff neck" was probably an infection, possibly due to a virus and that clinically the condition was distinct from Bornholm disease. Beeson and Scott (1941, 1942) tried to transmit the disease to volunteers, using throat washings and or blood taken from affected patients Throat washings had no apparent effect, but inoculation with blood appeared to produce the disease in some volunteers though the evidence was not conclusive. Attempts to infect laboratory animals and developing chick embryos failed.

Present Investigation

In the autumn of 1958 and again in the late summer of 1959 a small epidemic of acute myalgia principally affecting the trapezius muscles occurred among nurses at this hospital In all, 13 nurses reported sick—7 in the first epidemic and 6 in the second The total nursing staff at the main hospital numbers about 725 so the attack-rate seems very small. Inquiries among the nurses suggests, however, that many others were affected during the relevant periods but did not consider their symptoms severe enough to seek medical advice.

All except 1 of the 13 nurses who reported sick were admitted and the condition was studied more fully than appears to have been possible before.

CASE-RECORDS

Case 1—A 21-year-old nurse was admitted on Aug 7, 1958. For a day she had had severe pain in the neck which began suddenly and was aggravated by movement. She was in considerable pain and held her neck flexed to the right Though there was no true neck stiffness, all movements were restricted by pain. Both trapezius muscles were extremely tender to palpation over most of their extent, but there were no other abnormal physical signs and she was afebrile.

Progress—After admission there was slight intermittent pyrexia, of up to 99.6° F, for four days The pain in her neck gradually abated but six days after admission aching pain developed in both hands and both knees unaccompanied by stiffness or swelling These symptoms disappeared within twenty-four hours, and thereafter she was quite well

Case 4.—A 20-year-old nurse was admitted on Sept. 8, 1958 That morning she had suddenly experienced very severe interscapular pain spreading to both scapular regions, aggravated by movement and breathing She was in severe pain. Though there was no true neck stiffness all movements were restricted by pain, and both trapezius muscles were very tender to palpation There were no other abnormal physical signs and she was afebrile.

Progress—The pain in the neck remained severe for nine days, after which it gradually subsided. Seven days after admission the patient complained of pain in both knees and both ankles which lasted for four days, there was no associated swelling or restriction of movement The patient remained in hospital for twelve days and from the fourth day until discharge there was intermittent pyrexia of up to 100°F On discharge she was symptom-free.

Case 9—A 20-year-old nurse was admitted on Aug 3, 1959 For one day she had had vague abdominal aching and nausea On the day of admission aching developed in the neck, lower back, and legs She was afebrile. There was severe tenderness of both trapezius muscles, but no other abnormal physical signs.

Progress—A few hours after admission the patient's temperature rose to 101°F, but later on the same day it fell to normal again and remained so until the sixth day when it rose to 99°F She was discharged on sick leave, apparently cured, eight days after admission, but the following day she was re-admitted because of generalised muscular aches headache, and neck stiffness which had made her family doctor suspect poliomyelitis Lumbar puncture was now carried out, but the cerebrospinal fluid was normal in all respects After a further nine days during which she complained of transient fleeting muscular pains she recovered completely Throughout the second admission she was afebrile.

Case 11 —A 22-year-old nurse was admitted on Aug 6, 1959 For two days she had had generalised muscular aching, and on the day before admission occipital headache, mild *photophobia, and pain in the neck There was slight* photophobia and severe tenderness of both trapezius muscles There was no true neck stiffness, though all movements were restricted by pain No other abnormal physical signs were found, and the patient was afebrile

Progress —The day after admission severe trismus developed, this persisted for three days and then passed off This symptom was severe enough for tetanus to be suspected, particularly as there was a history of a small abrasion of the hand ten days before When the trismus passed off, the patient was quite well

The remaining cases are summarised in the accompanying table

INVESTIGATIONS

White-blood-cell counts were carried out in 11 of the 13 cases, and in 10 the total and differential counts were within normal limits In 1 case there was leucopenia (2,200 per c mm) with a normal differential count, and in this and 1 other case a few typical lymphocytes were seen, but Paul Bunnell tests were negative

The erythrocyte-sedimentation rate (Westergren) was measured in 10 cases, in 8 it was normal, and in 2 it was raised (25 and 27 mm in the first hour)

In 2 of the cases seen in 1958 specimens of stool collected within five days of the onset of symptoms were examined for the presence of Coxsackie viruses, by inoculation into suckling mice, with negative results

In 4 of the 1959 cases specimens of stool collected within five days of the onset of symptoms were examined for the presence of Coxsackie-B virus, adenovirus, poliomyelitis virus, or other cytopathogenic agents, by inoculation into Hela cell cultures, the results were negative In five cases complement-fixation tests on paired sera showed no evidence of recent infection with *Rickettsia burneti* or the following viruses influenza (A, B, C), parainfluenza 1 (Sendai), mumps, adenovirus, and psittacosis Streptococcal M G agglutination tests were also negative in all 5 cases Monkey-kidney tissue-culture neutralisation tests on the sera showed no evidence of infection with Coxsackie viruses B types 1-5

Discussion

In the epidemic illness described here the outstanding feature was the pain and tenderness affecting the trapezius muscles In 11 cases this was bilateral, and in 2 unilateral, its time of onset during the illness was inconstant

Other symptoms included mild transient aches in various muscles and joints in 10 patients, occipital headache in 5, dizziness in 2, pain in the masseter muscles in 2 (1 of whom had severe trismus), and colicky abdominal pain and nausea in 1 The illness lasted on an average for nine days, there was no evidence of inflammation of the throat or enlargement of cervical glands, constitutional upset was slight, and in most cases fever was absent or slight and short-lasting

The patients were all student nurses who shared the same dining-room with many others, but they did not all work in one particular department or ward or live in close proximity to one another

When the first patient presented with pain in the neck as the only symptom, its severity suggested a local spinal lesion, but the diffuse tenderness of both trapezius muscles, and later the onset of fever, and aches and pains elsewhere, pointed to some generalised disturbance, possibly a virus infection

In cases 2 and 3 pain in the neck was a late symptom, and initially the vague malaise and muscle and joint pains raised the possibility of influenza, or of mild acute rheumatism even though the affected joints were not swollen The absence of fever, however, was against either of these diagnoses, and in both patients acute rheumatism seemed even less likely when the erythrocyte-sedimentation rate proved to be normal

In some of the other cases the combination of muscular aching, headache, and neck pain presented a picture difficult to distinguish with certainty from pre-paralytic poliomyelitis, and indeed this diagnosis was seriously

DATA ON 9 PATIENTS

Case no	Age (yr)	Date admitted	Symptoms	Signs	Length of illness (days)
2	22	Aug 27, 1958	3 days vague malaise and slight aching in masseter muscles, 1 day pain in right knee and ankle, 1 day after admission giddiness, 6 days after admission pain in neck and shoulders, left wrist, and knee lasting 2 days	None on admission, 6 days later severe tenderness of trapezius muscles, afebrile	12
3	19	Sept. 6, 1958	3 days pain and stiffness in both knees and wrists, later transient muscle and joint aches, trapezius muscles painful for 1 day	Tender proximal interphalangeal joints, later tenderness of trapezius muscles, afebrile	13
5	22	Sept 10, 1958	2 days vague malaise, occipital headache, and pain in neck, 3 days after admission pain and stiffness in knees and wrists lasting 3 days	Severe tenderness of both trapezius muscles, temp 99 F on two occasions	8
6	19	Sept 12, 1958	Day of admission pain and stiffness of neck and occipital headache 4 days later transient aching both knees	Severe tenderness both trapezius muscles, afebrile	6
7	23	Sept 12, 1958	1 day general malaise, 4 days later pain and stiffness in neck	On admission temp 102 F, falling to normal after a few hours, but rising to 100 F on 5th day when both trapezius muscles were tender for 2 days	8
8	23	July 29, 1959	7 days occipital headache and pain in neck and shoulders, pain lasting 9 days (previous attack case 5)	Severe tenderness of both trapezius muscles, afebrile	16
10	19	Aug 5, 1959	1 day shivering aching in neck and legs, 2 days later pain and stiffness of neck	On admission temp 101 F, then 99 F for 4 days, 2 days after admission tenderness of left trapezius muscle	5
12	19	Aug 20, 1959	3 days severe pain in neck, gone when first seen	Slight tenderness of right trapezius muscle, afebrile	6
13	19	Aug 26 1959	1 day occipital headache and severe pain in neck dizziness and aching of legs	Severe tenderness of both trapezius muscles, afebrile	6

Cases 1, 4, 9 and 11 are described in the text entertained by another doctor who saw one of the patients (case 9) when she relapsed after discharge from hospital But the absence of any true neck rigidity, and the fact that fever was usually absent at the onset of the illness, made poliomyelitis unlikely

In a few patients the sudden onset of the muscular pain and its severity were reminiscent of Bornholm disease In the classical form this disease is characterised by the sudden onset of severe pain in the chest or upper abdomen, usually aggravated by breathing and often by swallowing, moderate pyrexia, and a pleural rub The illness may last for only a few days, or may run a lengthy or relapsing course

Pain or tenderness in the trapezius muscles has occasionally been encountered in Bornholm disease (Sylvest 1934, Ronald 1942, Nichamin 1945), but, of the patients so affected, severe pain in the chest or upper abdomen was the presenting or outstanding feature in almost all, fever of 102–103°F was not infrequent, and the erythrocyte-sedimentation rate was commonly raised

None of the patients described here had pain or tenderness in the chest or upper abdomen, only the trapezius muscles being affected to any significant degree The temperature remained normal throughout the illness in 7 of the 13 cases, and rose above 100°F in only 4 The erythrocyte-sedimentation rate was raised in only 2 of the 8 patients in whom it was measured

Thus there are several differences between this condition and classical Bornholm disease, and virological investigations did not support the latter diagnosis

The epidemic illness described here is probably identical with that described by Massell and Solomon (1935), Beeson and Scott (1941, 1942), Copeman (1944), and Wilson (1946), and probably also with the condition described by Warin (1956) as a variant of Bornholm disease

In all the cases described by these several workers, the clinical course of the illness did not differ significantly from that in present cases fever was unusual, the blood count was usually within normal limits, and the erythrocyte-sedimentation rate was normal in all the cases in which it was estimated, except for the second of two outbreaks described by Copeman (1944) when it was found to be raised in all 8 patients

In 5 patients of Beeson and Scott (1941, 1942), 1 patient of Copeman (1944), and 2 patients of Wilson (1946) persistent generalised "fibrositis" later developed In the present series this complication was not seen, but 1 patient had a relapse a day after recovering from the first attack, and 1 other had attacks during both epidemics

Conclusion

Epidemic "stiff neck" is an illness with features suggesting a virus infection, and it appears to be distinct from Bornholm disease

Summary

Two outbreaks of epidemic "stiff neck"—epidemic myalgia principally affecting the trapezius muscles—are described

The condition did not have the clinical features of classical Bornholm disease, not did virological studies support this diagnosis

The illness had features suggesting a virus infection, but the causal organism was not discovered

I am very grateful to Lord Evans, Dr W Tegner, Prof C F Barwell, and Dr F O MacCallum for helpful criticism and advice, and to Dr S E Reed, of the London Hospital department of bacteriology, and Dr D R Gamble and Dr C E D Taylor, of the Central Public Health Laboratories, Colindale, for the virological investigations

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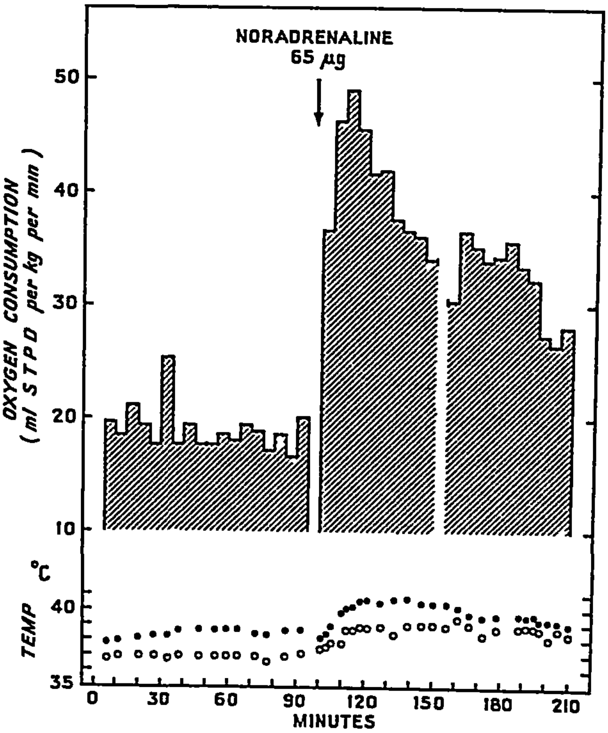
Preliminary Communication

POSSIBLE ROLE OF NORADRENALINE IN CONTROL OF HEAT PRODUCTION IN THE NEWBORN MAMMAL

On the basis of our experiments using the unanæsthetised cat, rat, mouse, and rabbit, we are suggesting that noradrenaline is secreted by the neonate in response to a lowered environmental temperature This noradrenaline raises the heat production of the animal and enables it to maintain its deep body-temperature

We are, at this stage, offering evidence only on the effect of noradrenaline on general heat production, and have not attempted to integrate this with other effects it may have on the animal's economy or to suggest the site of its action Shivering may also be involved to some degree in the production of heat



Calorigenic effect of noradrenaline in an unanæsthetised 5-day-old, 151 g kitten

At the arrow the animal was removed briefly from the metabolism chamber for a subcutaneous injection of noradrenaline 400 µg per kg Environmental temperature was 35°C, and the animal was in an atmosphere of approximately 21% oxygen, 79% nitrogen Temperatures were measured by thermocouples (closed circles, rectal, open circles, skin of back), and oxygen consumption, measured continuously, is plotted in the form of a 5 min histogram The break in the hatching indicates a two-minute interruption of the recording

Observe the rapid increase in oxygen consumption and the less rapid rise in body-temperature As all three values are rising together heat production must have increased

METHODS

The evidence consists in observations mainly carried out on the newborn kitten but supported in all main particulars in the rat, mouse, and rabbit (the guineapig is somewhat atypical in that adrenaline is also calorigenic) The animals were studied at 30°C or 35°C environmental temperature, before and after a subcutaneous injection of a ganglion-blocking agent (hexamethonium iodide 10 mg per kg body-weight) and/or *l*-noradrenaline (400 µg per kg) or *l*-adrenaline (400 µg per kg) Measurements were made of oxygen consumption and rectal and skin temperature in individual unanæsthetised animals Metabolism chambers of the Richards and Collison [1] pattern were used which allow continuous recording of oxygen consumption Temperatures were measured from thermocouples inserted into the rectum and applied to the skin of the back and pad [2] After a preliminary stabilisation period of about 80 min , the animal was removed, injected, and replaced and the observations continued

RESULTS

The findings were as follows

1 Hexamethonium at 30°C reduced heat production The oxygen consumption falls rapidly, and this is *followed* by a fall in deep and surface temperatures The reason for such an order of events must be a fall in heat production, not primarily an increase in heat *loss*

2 Hexamethonium at 35°C had little effect on oxygen consumption and heat production

3 Noradrenaline at 30°C had little effect in doses of 400 µg per kg in the normal kitten, but see (5) below

4 Noradrenaline 400 µg per kg at 35°C increased oxygen consumption and heat production (see accompanying figure) The order of events and the rise in skin temperature show that a rise in oxidative heat production must precede the rise in body-temperature [3]

5 Noradrenaline at 30°C reversed the changes set in motion by hexamethonium, but hexamethonium at 35°C did not prevent the rise in heat production caused by noradrenaline

6 Subcutaneous adrenaline (400 µg per kg) or subcutaneous saline (0 9% sodium chloride, 4 0 ml per kg) had little or no action as thermogenic agents in the neonate

7 Age altered the responses to both hexamethonium [4] and noradrenaline Maximal effects were found in the first few days of life, and little action was observed by the age of 5–7 weeks in the cat and 3–4 weeks in the rat

DISCUSSION

We interpret these findings as meaning that at 35°C there is little or no natural secretion of noradrenaline the animal is in the so-called zone of thermal neutrality and its oxygen consumption is low Hexamethonium is, under these circumstances, not preventing the release of noradrenaline, so blockade does not alter heat production At 30°C however, there is normally some secretion of noradrenaline and the animal has a higher oxygen consumption and heat production This rise of metabolism at a lower temperature is a well-known phenomenon Consequently, at 30°C hexamethonium blockade will deprive the animal of its normal calorigenic stimulus, and heat production will fall

Noradrenaline at 30°C will not be calorigenic unless the dose injected, and the amount absorbed from the injection site, is sufficient to raise the blood concentration above its existing level Less than this will be " buffered " by a cutting down of normal secretion This " buffering ", however, is impossible if, on account of a high external temperature, no secretion is taking place Therefore, at 35°C injected noradrenaline is calorigenic Heat production and temperature gradients (deep body to environment) increase to values normally associated with a lower environmental temperature

CONCLUSION

We feel that the most likely explanation of the results is that the neonate of some species normally depends upon the secretion of noradrenaline to keep it warm It is interesting that noradrenaline should be cast in this rôle, as in the adult it is considerably less calorigenic than adrenaline [5] Only in the experiments of Hsieh et al [6 7] and Depocas [8] has the reverse been shown, and then only in the anæsthetised, cold-adapted adult rat However, our results may perhaps point to a function for the large amount of chromaffin tissue known to be present in the newborn of many species, and its relatively high content of noradrenaline Although we have, as yet, no information on the point, it seems to us not unlikely that the human infant could also have similar reactions In this event, the implications in pædiatrics are self-evident, and we would be extremely interested to hear of relevant clinical evidence

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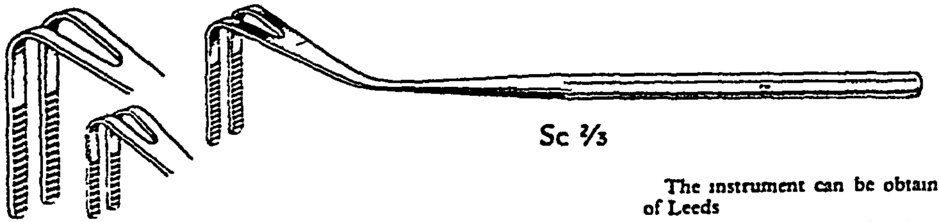
New Inventions

NEW RETRACTOR FOR HAND SURGERY

Satisfactory retraction in hand surgery is sometimes difficult to obtain, particularly as the standard retractors are far too large



Full Size Ends

The retractor shown in the accompanying figure has been found very useful in cases, such as Dupuytren's contracture, where dissection is being carried out by undercutting The instrument is $5^1/_2$ in long, and the blades are 1 in long A smaller model with $^1/_2$-in blades is also obtainable The part of the handle nearest the blades is angled backwards, so that the line of pull is opposite the centre of the blades The blades are at right-angles to the line of pull, their upper surface is notched to prevent slipping Gentle retraction is possible, with a direct pull at right-angles to the skin surfaces, this does not roll up the skin edges, and does not greatly obstruct the view

The instrument can be obtained from Chas F Thackray Ltd , of Leeds

H Graham Stack
F R C S

Albert Dock Fracture and Orthopædic
Hospital, London, E 16

Reviews of Books

Biochemical Aspects of Neurological Disorders

Editors J N CUMINGS, M D, F R C P, professor of chemical pathology, Institute of Neurology, London, MICHAEL KREMER, M.D, B SC., F R C P, consultant neurologist, National Hospital, London *Oxford Blackwell Scientific Publications 1960* Pp 230 *37s 6d*

THIS timely and useful production outlines the biochemical background and the clinical picture in a number of neurological diseases at present thought to be due primarily to biochemical lesions The exposition of the purely biochemical aspects is particularly useful since it allows the general principles to be considered and invites their application to disease processes of still unsettled ætiology The book is of a generally high standard and the presentation is admirably clear

Sir Charles Symonds has been a pioneer among clinicians in emphasising the importance of the biochemical lesion in neurology Appropriately, therefore, he contributes a thoughtful and thought-provoking review of demyelinating diseases, in which he draws together the established clinical and pathological facts which must be accounted for in any explanation of biochemical mechanisms Among much that is excellent, Dr W W Payne's discussion of calcium and phosphorus metabolism and Prof N F Maclagan's consideration of the biochemistry of coma are particularly interesting The chapter on the biochemistry of muscle disorders by Dr Brian McArdle is valuable both for the review of what is known and for the clear exposition of unsolved problems Dr J St C Elkington's succinct account of the clinical aspects of porphyria emphasises the value of symptomatic treatment where natural remission from an attack is so likely

This book will appeal widely to clinicians, and it may surprise some to find that such a variety of biochemical lesions are already clearly recognised in neurology for others the detailed outline of the chemistry involved will add to their understanding and handling of the clinical condition

A Guide to the Identification of the Genera of Bacteria

V B D SKERMAN, B AGR SCI, reader in bacteriology and head of the department of bacteriology, University of Queensland Baltimore Williams & Wilkins London Baillière, Tindall, & Cox 1959 Pp 257 44s

BACTERIOLOGISTS sometimes have difficulty in naming unfamiliar organisms which they isolate This applies seldom to the well-known pathogens of man, animals, and plants, which are easy to recognise, but to commensal or saprophytic organisms which sometimes colonise or merely contaminate pathological lesions or may be found in natural materials examined in the laboratory Matching the identifying characters of unknown with known isolates by hunting through the pages of *Bergey's Manual* or a major textbook is not perhaps the most orderly or satisfying way of meeting this difficulty, although it is certainly the commonest To help bacteriologists with this problem Mr Skerman has devoted much patient labour to preparing a comprehensive key to the genera of bacteria After having determined the characters of the unknown organism, the bacteriologist begins at the beginning of the 48-page key, and reads through it until he reaches the point at which he can identify his organism As he reads, he answers a series of questions which the key puts to him in a defined order As each question is answered, the key supplies the number of the next section to be consulted until finally a generic name is given along with the next number to be consulted Thus, the key puts the bacteriologist more quickly than he could otherwise expect in touch with the genus in which he will finally identify the species of his troublesome organism From that point the key is used along with standard texts or manuals assisted by the Guide's own digest of genera (largely, by agreement, from *Bergey's Manual*) and by use of its own methods for carrying out tests of value in identification

This interesting volume will have to be tested by use before its value may be finally assessed Meanwhile it may be welcomed for what it seeks to do, even if its place in medical laboratories may not be so readily assured as in laboratories devoted to other parts of bacteriology

Diagnosis in Locomotor Disorders

KENNETH STONE, D M, M R C P, physician, Arthur Stanley Institute for Rheumatic Diseases, The Middlesex Hospital London Oxford University Press *1960* Pp 224 *25s*

THE art of differential diagnosis scorns the artificial frontiers drawn round the specialties of medicine, and the merit of a book which deals with it can be measured by the freedom with which its author roams across these boundaries By this standard Dr Stone has done well he has applied himself not only to conditions which produce pain, deformity, inflammation, or defective function in the locomotor system but also to peripheral vascular diseases, involuntary movements, and paræsthesiæ The book is arranged in part on a regional basis, dealing with the differential diagnosis of pain in specific joints or areas, partly in sections devoted to individual signs or symptoms The reader is guided past the pitfalls which await the unwary—the patient whose " rheumatism " is really metabolic bone disease, the arthropathy which is not rheumatoid arthritis but indicates a bronchial carcinoma Many readers will be grateful for help, which standard textbooks often fail to give, on subjects such as acroparæsthesiæ The book is liberally illustrated with radiographs, these have been well chosen, but the reproduction (positive in some, negative in others) is not always adequate An appendix gives the normal values for a selection of laboratory tests

In a book modest in size and price Dr Stone has provided a useful and practical guide which general practitioners and specialists of many kinds will welcome.

The Cell of Schwann

GILBERT CAUSEY, M.B, F R.C.S, professor of anatomy, Royal College of Surgeons of England Edinburgh E & S Livingstone 1960 Pp 120 21s

THIS small book has a somewhat deceptive title which suggests at first glance that its scope is very restricted In fact a great deal of ground is covered and much interesting and up-to-date information is recorded about the structure of peripheral nerves, their degeneration and regeneration, and even their tumours The author has himself done much research work on nerves, using laboratory animals and studying nerves not only with the light microscope but with the electron microscope The pictures and diagrams are easy to decipher, even by one not expert in electron microscopy The brief historical section is pleasantly informative Among the spate of short monographs which are pouring out at present this one is well worth reading by all those interested in the nervous system

Auscultation of the Heart

ABE RAVIN, M.D, associate clinical professor of medicine, University of Colorado School of Medicine Chicago Year Book Publishers London Interscience 1959 Pp 166 45s

A SHORT volume on clinical auscultation of the heart is welcome, and this is in fact probably the best of the few short monographs on this subject

The general principles of sound and of phonocardiography are briefly discussed and adequate phonocardiograms are used to illustrate the text, although the author sensibly makes it clear that a phonocardiogram is only as good as the person who takes it The book is to be strongly recommended for its subject matter and its clear presentation, and it is well written Close reading, however, reveals some occasional surprising statements, which are more conspicuous because of the generally high level of the text. Despite modern views to the contrary, it is stated that the heart is always enlarged in acute rheumatic carditis and that this is responsible for the mid-diastolic rumble The timing and pattern of systolic murmurs do not seem to receive sufficient emphasis The murmur of ventricular septal defect is described as diamond-shaped while it is in fact pansystolic, and no mention is therefore made of this useful method of distinguishing a ventricular septal defect from a short-ejection innocent systolic murmur The section on gallop rhythm is confusing, mainly because of the perpetuation of the term "protodiastolic" (protodiastole begins in systole) for the third heart-sound, which is thought not to be physiological on other grounds There is confusion between atrial and third sounds, for gallop rhythm is said to be rare in atrial fibrillation It should be clearly stated somewhere that an atrial sound, though abnormal, is not evidence of failure, while the third sound in older subjects is good evidence of raised atrial pressure

A Short Synopsis of Human Protozoology and Helminthology

L R S MACFARLANE, O B E , M D , D P H , professor of pathology, Royal Army Medical College, London Edinburgh E & S Livingstone 1960 Pp 251 35*s*

THIS book is based upon the class-notes issued in the author's department at the Royal Army Medical College It is mainly an epitome of Craig and Faust (and there could be no better source of accurate information), which means that the emphasis is zoological rather than pathological As a companion to lectures and laboratory classes it will help many students to identify and describe accurately the commoner protozoa and worms parasitic on man, but those who want to know more than a smattering about the reactions of the body to infestation or the related problems of epidemiology must seek elsewhere The illustrations (by R M Leach) are good Colour photography may ultimately surpass the best water-colour, but it has not done so yet It is a pity that the small size of the book makes it necessary to print the captions on the reverse of some of the plates The line drawings would be improved if there was some indication of their scale Some emphasis is placed upon the differences in pigment produced by the species of plasmodium, but it is not clear from the text where this pigment may be seen Hydatid disease occurs in many other places than those listed There is no evidence that trichomonal vaginitis can be cured by changing the pH of the vagina (already often as low as 5 2) and antibacterial measures The symptoms attributed to whipworms seem exaggerated in the light of common experience Threadworm, the common English name for *Enterobius vermicularis*, does not appear in the index The technical appendix is clear, but if this book is used outside the classroom (as it certainly will be) the procedures mentioned in the text (e g , concentration methods for fæces) should be included The printing is not really a success because only one size of capitals has been used (and that rather too large for the page) and because italics are used without any consistent rule, *it is hard to find one's way in the text and the book is tiring to read*

On the Threshold of Delinquency

JOHN BARREN MAYS, M A Liverpool Liverpool University Press 1959 Pp 243 25*s*

THIS book is essentially the story of an evening club for selected boys, age 8 to 13, living in a slum district of a seaport city, seemingly Liverpool, the club deliberately planned to have a majority membership of actual or likely lawbreakers The book describes and analyses the venture's first four "experimental" years, with detailed accounts of many of its members and their response—or lack of response—to its attempts to help them by collective and individual means ("groupwork" and "casework") The club was designed to attempt a rough estimate of the parts played by personal emotional disturbance and by domestic and local environment, including locally accepted values and behaviour, in the making of young delinquents, and with the confessed hope that the latter influences might be found to predominate in many cases and might respond to treatment less recondite, individual, and costly than that of the psychiatrist and child-guidance clinic

It may seem surprising that any inquiry should be necessary to show that environmental influences so obviously powerful as those described in a chapter on "the subcultural background" are in fact powerful, but if it was needed, here it is Here also is evidence that if and when all the people in authority, notably parents, can be induced to work together for good, then good may be expected, and that to induce them so to work is extremely difficult The book should interest both social workers and those able to influence or alter the environment in which thousands of our fellow citizens are born and grow to maturity

The Care of the Aged in Norway

FINN DANIELSEN Oslo Norwegian Joint Committee on International Social Policy London Bailey Bros & Swinfen 1959 Pp 56 6*s*

IN common with the rest of Western Europe the Norwegians face the problem of a rapid increase in the numbers of old people, both absolutely and in proportion to the population as a whole Their solutions are broadly similar to our own, though the distinction between hospitals and welfare hostels is not apparently as clear as it is in this country The Norwegians believe in helping old people to live in their own homes as long as possible, but it sounds as if their system of home-helps is less highly developed than our own Special importance is attached to old people's housing

The Scandinavian countries have a reputation for treating their old people generously in the matter of pensions, but it is hard to compare the schemes described in this book with the systems of old-age pensions supplemented by National Assistance used in this country

The book is ably written and profusely illustrated The pictures probably show the best rather than the typical, but they suggest that before long Norway will be second to none in her arrangements for the care of the aged

Significant Trends in Medical Research (*Ciba Foundation Tenth Anniversary Symposium* London J & A Churchill 1959 Pp 356 50*s*)—The Ciba Foundation celebrated its tenth anniversary by a special colloquium which must have been a stimulating experience for those privileged to attend, and, edited by Dr G E W Wolstenholme, Miss Celia M O'Connor, and Miss Maeve O'Connor, makes fascinating reading The speakers were *distinguished specialists, some of them Nobel prize-winners*, and the subjects discussed ranged from molecular structure to kwashiorkor There were papers on the pyridine nucleotide enzyme complexes, virus multiplication, population dynamics of body cells, genetics, neurophysiology, the mechanism of action of hormones, insulin, pulmonary disease, malignant transformation, hypertension, and medical research in the United States The speakers were asked to pick out those developments in their special fields in the past few years which they thought would prove to be the most significant in the next. This good idea gave rise to some very interesting thoughts and discussion, for the future was in the minds of the participants all the time

There are some generalisations here and there, and strivings after generalisations, which should inspire teachers and investigators and direct them in the way they ought to go This is a book to keep, for it will be splendid reading for years, and it will have a historical value for all time

Proceedings of the First International Congress of Neurological Sciences (*Vol III Electroencephalography, Clinical Neurophysiology, and Epilepsy* London and New York Pergamon Press 1959 Pp 707 £7)—The First International Congress of Neurological Sciences was held in Brussels in July, 1957 Though it must have been one of the largest specialist congresses ever held, this did not daunt the secretary-general, Dr Ludo van Bogaert, and Dr J Radermecker from tackling the formidable task of editing the proceedings This is the first of five volumes to appear and contains 135 papers The text is 'Varityped', with abundant recordings, charts, and some plates

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Laboratory Manual of Pediatric Micro-Biochemical Techniques—In our review of May 7 we stated incorrectly that this book is published in London by H K. Lewis The University of Colorado Medical Press are the sole publishers

THE LANCET

LONDON 11 JUNE 1960

Too Many Calories

WHILE a large section of the world's population subsists on an inadequate diet, in other communities excessive intake of calories gives rise to serious medical and social problems The Food and Agriculture Organisation of the United Nations has been created to deal with international undernutrition the pharmaceutical industry continues to seek means of saving the victims of their own appetites from the consequences of overeating, and surgeons are devising operations for the removal of unwanted fat[1]

In a recent symposium at the Mayo Clinic, GASTINEAU[2] concluded that "no definite metabolic abnormality has been demonstrated as a cause for human obesity" This cannot be denied, but recent developments—for example, the work of CHALMERS and his colleagues at the Middlesex Hospital—have brought a little light In 1958 these workers[3] reported the presence of fat-mobilising activity in the urine of healthy people who had been fasting, and that this activity could not be detected when obese subjects were given 1000-calorie diets containing 90% carbohydrate, whereas it was enhanced when the diet contained 90% fat A further report[4] from the same department describes the purification and properties of the material responsible for these effects Subcutaneous injection into mice of urinary extracts from subjects on a restricted carbohydrate intake or fasting was followed by a fall of blood-sugar, while the blood lipids and ketones, as well as the liver-fat concentration, increased When a series of injections was given, the animals lost weight without their appetites being affected, and the loss of weight was found to be due to reduction in the body fat and water content, the protein content apparently remaining unchanged Since this activity could not be detected in the urine of patients whose pituitaries had been damaged or removed, the Middlesex group suggest that the material responsible is of pituitary origin They remark that, of the hormones known to be produced by the pituitary, the material in the urine extracts most closely resembles corticotrophin

Meanwhile the problem of managing the overweight patient remains, and the plethora of advice is some measure of the failure of any simple method of management to produce consistently successful results Two double-blind trials in Edinburgh on the comparative value of phenmetrazine hydrochloride and other drugs in the management of obesity are reported in this issue Dr DUNCAN and his colleagues (p 1262) studied "refractory" obesity in a group of patients, diabetic and non-diabetic, who had been under observation for at least a year, and who despite dietetic advice had failed to lose weight in the three months preceding their admission to the trial Two drugs were tested in contrast to the findings of YUDKIN,[5] methyl cellulose was found to be without effect, but phenmetrazine, administered for eight weeks in the doses usually recommended, was associated with a greater rate of weight loss than that in periods in which dummy tablets were given. Dr HAMPSON and his colleagues (p 1265) compared the value of phenmetrazine, dexamphetamine, and control tablets in the same patients, and concluded that both the drugs had some value in accelerating loss of weight. They noted, however, that the rate of weight loss diminished as the trial continued, whether the drugs or the control tablets were being used

The controversy created by BANTING in 1863[6] has been renewed from time to time—most recently by KEKWICK and PAWAN[7] They showed that obese patients lost more weight when consuming diets containing 90% fat than when the diets were predominantly of protein or carbohydrate The periods of study were short, amounting to less than ten days in each patient Two further investigations on similar lines indicate that the usual rapid fall in weight when a diet with a high fat content is consumed is due to changes in body-water content rather than to any change in calorie requirements or expenditure OLESEN and QUAADE[8] studied eight obese women who remained on a high fat and low carbohydrate intake for periods of nine to twenty-two days, with an initial control period on an unrestricted diet, and a later period on a diet with a high carbohydrate content On the high-fat regimen considerable initial loss of weight was soon followed by restoration of equilibrium, and weight continued to be lost at a rate in keeping with the calorie content of the diet, whatever its chemical nature PILKINGTON and his colleagues[9] studied the losses of weight of nine very obese patients who were maintained on constant diets providing 800–1000 calories daily, predominantly either fat or carbohydrate They showed convincingly that when the diet is changed from a high fat to a high carbohydrate content, with the total calorie intake kept constant, then weight is gained Change to a high fat intake led to relatively sudden loss of weight in ten days patients might lose as much as 2 5 kg in excess of the anticipated loss, but thereafter their loss of weight continued at the same steady rate whether their diet was provided mainly from fat or from carbohydrate These sudden gains and losses of weight with changes in diet they attributed to changes in fluid balance

Some evidence on this point has been published by FURNASS,[10] who measured oxygen consumption and carbon-dioxide excretion continuously for periods as long as twenty-four hours He studied subjects previously "saturated" with carbohydrate, and compared the effects of giving 1000 calories as dextrose or as cream When the cream was given the respiratory quotient (R Q), as expected, was 0 7, but, on the other hand, when the dextrose was given the R Q did not rise to unity, as might have been foretold on the basis of complete combustion of the carbohydrate FURNASS continues

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[1] Clarkson, P *Brit med J* 1959, ii, 1334

[2] Gastineau, C F *Proc Mayo Clin* 1960, 35, 119

[3] Chalmers, T M, Kekwick, A, Pawan, G L S, Smith, I *Lancet*, 1958, i, 866

[4] Chalmers, T M, Pawan, G L S, Kekwick, A *J Endocrin* 1960, 20, 21P

[5] Yudkin J *Lancet* 1959, ii, 1135

[6] See *ibid*, 1958, ii, 785

[7] Kekwick A, Pawan, G L S *ibid* 1956, ii, 155

[8] Olesen, E S, Quaade, F *ibid* May 14, 1960, p 1048

[9] Pilkington T R. E, Gainsborough, H, Rosenoer, V M, Carey, M *ibid* April 16, 1960, p 856

[10] Furnass, B *J Physiol* 1959, 150, 11P

> "when computations were made in terms of element balance, it appears that up to 50 g per day of oxygen consumed may not have been used for combustion in the accepted sense of the word These observations are compatible with the hypothesis that unexpectedly low respiratory quotients may represent the combinations of some absorbed oxygen with hydrogen atoms in depot fat, thereby resulting in desaturation of the fat with change in its physical properties It is suggested that such a mechanism could reflect a process of adaptation to the external environment, a possibility that cannot be detected by applying the commonly accepted concepts of indirect calorimetry"

This important work may provide a key to some of the problems raised by the studies with high fat and high carbohydrate diets to which we have referred

Appetite is particularly difficult to study in man, but perhaps some of the successes claimed in the past for various types of diet have been due to their effect on appetite, or even perhaps on activity—a factor commonly ignored Certainly there is still no reliable evidence that changes in diet of the type described alter the efficiency with which the body derives its energy from the food consumed If appetite can be controlled by a high fat diet or some other modification with a high satiety value, this might be more effective than attempting to persuade the obese to practise dietary continence As regards appetite-controlling drugs, the two articles we publish today confirm that phenmetrazine and dexamphetamine have some limited value But with both drugs there is danger of addiction[11], and phenmetrazine has now been added to the list of Schedule IV substances so that it can no longer be obtained without a prescription There is still an unfilled need for a drug which is consistently reliable, safe, and cheap

Surgical Treatment of Pancreatitis

THE pancreas, lying securely ensconced on the back wall of the abdomen, offers a therapeutic challenge to surgeons which is now being taken up

Pancreatitis is perhaps best considered under the headings "acute" and "chronic relapsing"—though, as SINCLAIR[12] has pointed out, "acute pancreatitis" covers a wide range of conditions, from the most fulminant of abdominal emergencies to subclinical disturbances detectable only by biochemical measurements Clinically acute pancreatitis simulates visceral perforation very closely[13] In pancreatitis the pain may be more agonising, but the abdominal rigidity is not so general or so constant Cyanosis and slight jaundice are commoner in pancreatitis, it usually occurs in fat subjects, and there is a definite alcoholic history in a fairly high proportion of cases—up to 25% in American series[12] The discoloration of the flanks (Grey-Turner's sign) and discoloration at the umbilicus (Cullen's sign) do not become evident early enough in the disease to be of practical value in distinguishing between acute pancreatitis and a perforated peptic ulcer for the purpose of managing acute pancreatitis without operation.[13] The serum-amylase level is raised initially, and gross elevation is almost pathognomonic, but in perforation of a peptic ulcer and in other abdominal conditions the serum-amylase may be raised to comparable levels[13] Urinary diastase is usually increased, and glycosuria may be found, diabetes may result[14] In the important new field of X-ray investigation of the acute abdomen by means of oral contrast media, SAMUEL[15] has described widening of the C curve of the duodenum, forward displacement of the stomach, and changes in the duodenojejunal flexure produced by the acutely inflamed pancreas

In the treatment of acute pancreatitis, operation is usually avoided in the first instance unless it is needed to establish the diagnosis Where the diagnosis is in doubt, laparotomy is best undertaken, and it probably does not increase the mortality in the early stage If the abdomen has been opened and acute pancreatitis found, the biliary system may usefully be decompressed, for, whatever pressure differential may have existed between the pancreatic and biliary ducts before treatment is begun, the deliberate inhibition of pancreatic secretion, which is part of the therapeutic programme, will reduce pressure in the pancreatic ducts below that in the biliary tree and so favour the reflux of bile ELLIOTT et al[16] have emphasised the importance of emptying the biliary tree of any mixture of bile and pancreatic juice—a mixture which they have shown to be particularly virulent—and choledochostomy or cholecystostomy is therefore a sound procedure This procedure is also anatomically sound almost always in acute pancreatitis the pancreatic and bile ducts are found to have a common opening in the duodenum—this arrangement was found in 20 of 21 fatal cases in SINCLAIR's[12] series

Whether the abdomen has been opened or not, restoration of blood-volume is essential, much fluid can be lost from the circulation by the widespread retroperitoneal inflammatory exudation[17] Some clinicians advocate the use of cortisone or corticotrophin for its effects on the shock and its anti-inflammatory effects For reduction of the secretory activity of the pancreas continuous gastric aspiration should be applied, in order to remove gastric hydrochloric acid, which, through the secretin mechanism, has a powerful stimulant effect on the pancreas Drugs which actually inhibit pancreatic secretion, such as atropine or propantheline, should be administered, there is some experimental evidence that hexamethonium is slightly more effective,[18] and propylthiouracil has also been used [19] For the relief of pain pethidine is preferable to morphine because it causes less contraction of the duodenum If the patient is not shocked, nitrites help by relieving spasm of the sphincter of Oddi Epidural and splanchnic block have been advocated for relief of severe pain, and have been claimed to have a beneficial effect on the cause of the disease by improving the blood-supply to the pancreas [20]

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[11] See Times Jan 19 1960

[12] Sinclair I S R J R C Surg Edinb 1959, 5 57

[13] Cope, Z The Early Diagnosis of the Acute Abdomen London 1946

[14] Cattell R B, Warren K W Surgery of the Pancreas Philadelphia 1953

[15] Samuel E Brit J Radiol 1960 33 82

[16] Elliott, D W, Williams, R D, Zollinger R M Ann Surg 1957, 146 669

[17] Keith, L M Jr, Watman R N Surg Forum, 1955, 5, 380

Acute pancreatitis, including the rare postoperative variety, is a highly lethal condition If the patient survives the early phase he may die later when the pancreas has become simply a mass of infected slough In cases, therefore, which are hanging fire or deteriorating with recurrent pyrexia, surgical drainage of the peripancreatic tissues (which has nothing to offer in the early stages) and excision of sloughs may be lifesaving The administration of antibiotics to control secondary infection is important throughout the treatment of acute pancreatitis, and one of the tetracyclines is generally employed for this purpose

The management of the patient with relapsing pancreatitis is controversial and will probably remain so until the underlying causes are better understood [21] Many different procedures have been advocated, and a balanced view has been given by **Rodney Smith** [22] In chronic relapsing pancreatitis the pancreas is especially vulnerable, and if, anatomically, biliary reflux is possible and likely to precipitate further acute episodes it is rational to divert the bile from the pancreatic duct This can be done by sphincterotomy, in which the "common channel" is laid open so that the common bileduct and pancreatic duct open independently into the duodenum The operation is best done under direct vision after anterior duodenotomy [22] The length of the incision dividing the sphincter is usually 4–5 mm **Bartlett** and **Nardi** [21] recommend more extensive division of the posterior duodenal wall and the anterior wall of the common duct proximally for 1 5 cm, dividing not only the common sphincter of both ducts at the end of the papilla but also the muscular sling within the duodenal wall, described by **Boyden**,[23] which also surrounds both ducts Sphincteroplasty with mucosal suture, by various methods and sometimes with a wedge resection of the sphincter, is preferred by some surgeons [24] Sphincterotomy, laying open the common channel, exposes the duct of Wirsung, which can then be catheterised and operative pancreatograms obtained [22] **Bartlett** and **Nardi** [21] have carried out sphincterotomy and transduodenal exploration of the pancreatic duct in 53 cases, recently adding pancreatography as a standard part of the procedure In these operations anatomical variations in the definition of the ducts must be remembered, the accessory duct of Santorini may be the main pancreatic duct, and if stenosed may have to be enlarged [21]

Distal pancreatectomy and retrograde ductal drainage, by removal of the pancreas distal to the neck together with the spleen, clearance of stones from the duct system in the remaining head, and anastomosis of the divided duct to a jejunal Roux loup, secures retrograde drainage **Aird** and **Buckwalter** [25] have described the operation of removing the left part of the gland and implanting the cut end into a Roux loop of jejunum **Aird** emphasises the title "retrograde pancreaticojejunostomy" for this operation rather than "caudal pancreaticojejunostomy", for, as **Ross** [26] showed, the tail of the pancreas is a very short and somewhat variable structure In many cases, however, the head of the gland is the main site of the disease, drainage of the main duct, leaving the choked smaller ducts and acini, proves inadequate, and pancreatoduodenectomy must be considered—though, unless there is a definite suspicion of malignancy, most surgeons would think twice before embarking on this formidable procedure

Pancreatojejunostomy—anastomosis in continuity of the duct of Wirsung to a jejunal loop—has been recommended by some [14 27] Pancreatic denervation, though without effect on the pancreatitis itself, is worth considering in view of its effect in relieving pain, direct nerve section of the branches coming from the right and left cœliac ganglia to the head of the pancreas can be carried out. In certain cases, when a firm thickening is encountered in the pancreas, associated with jaundice, the older operation of cholecystenterostomy, by relieving tension in the biliary tract, may prove worth while [28]

Annotations

SHORTAGE OF RADIOGRAPHERS

THE shortage of radiographers in the National Health Service has been causing much anxiety for several years Admittedly recruitment has improved somewhat, but wastage is very great A large majority of new students are women, of whom some never qualify and many leave soon after qualification to marry or to do other work It is estimated that a third of all qualified women radiographers leave within a few years of completing their training and only a few ever return There is now a shortage in establishment in England and Wales of about 500 radiographers, and this is seriously impairing the efficiency of hospital radiological departments The Ministry of Health appointed a study group to investigate the shortage and to determine its causes The report of the group has now been received and certain suggestions [29] have been put by the Minister of Health to hospital authorities

The shortage is unevenly distributed and is greatest in remote and unattractive districts In some areas the main cause is still the lack of training facilities, and regional boards are advised to review their training arrangements, in consultation with the teaching hospitals, to see whether additional schools can be provided But staffing is unsatisfactory even in many areas with excellent training schools, and all regions are more or less understaffed The position tends to be worst in prosperous industrial areas of the North and Midlands where there are many attractive openings for young people and strong competition from industry for male and female labour

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[18] Palmer, J D *ibid* 1952, i, 560
[19] Reid, L C, Paulette, R E, Challis, T W, Hinton, J W *Surgery*, 1958, 43, 538
[20] Marion, P *Lyon chir* 1945, 40 315
[21] Bartlett, M K, Nardi, G L *New Engl J Med* 1960, 262, 643
[22] Smith, Rodney, *in* Recent Advances in Surgery (edited by S Taylor) London, 1959
[23] Boyden, E A *Surg Gynec Obstet* 1959, 108, 641
[24] Jones, S A, Smith, L L, Gregory, G *Ann Surg* 1958, 147, 180
[25] Aird, I, Buckwalter, J See I Aird, *Lancet*, 1957, i, 1199
[26] Ross, J A *ibid* 1957, ii, 45
[27] Duval, M K, Jr *Surgery*, 1957, 41, 1019
[28] Edwards, H C *in* Recent Advances in Surgery London, 1954
[29] Memorandum H.M (60)28

The study group found that vigorous local publicity to attract students was often successful, and they recommend advertisements in local papers, talks by the radiologist or the superintendent teacher of radiography to upper forms of local schools, and the holding of "open days" at local hospitals at which schoolchildren could see at first hand the work of the radiographer and the X-ray department The Minister hopes that by wider publicity and by the extension of training facilities the recent improvement in recruitment will be carried further, and that more men will enter the service (this is vital if the more senior posts are to be staffed and maintained)

The Ministry memorandum refers to apprehension among students and their parents about possible dangers of radiation Good publicity methods could counteract the sensational statements that appear from time to time and explain the very strict regulations now in force for the protection of staff and patients Unsatisfactory working conditions and staff relationships and inadequate amenities are sometimes contributing to staffing difficulties, and hospital authorities are urged to do everything possible to improve conditions A constant source of dissatisfaction among radiographers is the increased pressure of work, aggravated by staff shortages and the stress of emergency calls The Minister suggests that hospital medical committees draw up criteria to assist junior medical staff in deciding when to call for an "emergency" X-ray examination, bearing in mind the general recommendations in part III of the interim report of the Adrian Committee on radiological hazards, concerning technical aspects and administrative arrangements to minimise the number of X-ray examinations The Minister also hopes that hospital authorities will do everything possible to encourage married women to return to the service, either part-time or full-time, when their family commitments allow An increase in the maximum rates of grant for student radiographers has been announced by the Ministry

Salary scales and promotion prospects are not mentioned in the memorandum, though these are the most important means of stimulating recruitment and maintaining adequate staffs After long negotiations and arbitration new scales were agreed in August, 1959, which are a considerable improvement The starting salary of £500 is attractive to a young woman on qualifying but less so to a family man with many other opportunities in industry The maximum points in all grades are too low and there is often little or no prospect of promotion for many years An increase in the establishment of senior-radiographer posts would provide more incentive, and more appointments as superintendent radiographer (grade 1) would encourage young men to remain in the service Even in the superintendent-radiographer grades the maximum salaries are still too low and compare unfavourably with those in the administrative grades of the National Health Service of comparable seniority and responsibility, and a recent arbitration award for administrative and clerical staff has further increased the differentials Substantial increases are required in the higher grades if the quality of the service is to be maintained and improved and if men of ability and initiative are to remain in the X-ray departments and become teachers in training schools In this respect regional hospital boards might be given more discretion to provide larger additional allowances for special qualifications or responsibility, particularly in large training schools

The Faculty of Radiologists also considered in detail the causes and consequences of the shortage, in their memorandum of December, 1959 They drew attention to the very grave situation in many departments where there is serious overwork, inadequate supervision of junior staff, and an inevitable lowering of standards The difficulty of obtaining locums during holidays and sickness has been so great in some places that the services of private X-ray firms have had to be called upon The faculty emphasised that radiographers are carrying out important, skilled, and responsible work and their status and conditions of work require special consideration Among other constructive proposals are suggestions for revising and simplifying the syllabus and stimulating clinical interest, more generous training grants, and a special living allowance in addition to a training grant for students wishing to train and then work in an isolated district. Some form of additional incentive payments might well encourage qualified radiographers to take up posts where the need is greatest Another suggestion is that students should be accepted at 17, and some training schools already have junior assistant posts in which girls leaving school are given paid work in the X-ray department until they are old enough to begin the course

Drastic and vigorous action is necessary if the crisis is to be resolved, and it may well be that a combination of these proposals will be necessary for success

TREATMENT OF DIABETES INSIPIDUS

CHLOROTHIAZIDE and certain of its analogues have proved effective in the treatment of diabetes insipidus Crawford et al[1] administered chlorothiazide 1 g or hydrochlorothiazide 0 1 g (doses for adults) daily by mouth in three or four divided doses to seven patients with this condition, and showed that these drugs increased urinary solute and decreased urinary flow Within two hours of ingestion of the drugs excretion of sodium increased abruptly, and later that of potassium Excretion of chloride increased and urinary pH rose Although an increase of urinary flow was not a regular finding, in the first six hours excretion of water usually exceeded fluid intake, and up to about 1 kg body-weight was lost in the first twenty-four hours The excretion of sodium began to decline within eight hours after treatment was started, and of potassium within fifteen hours Potassium deficiency invariably developed but was readily overcome by giving potassium chloride orally in a dosage of 3 g daily throughout the period of treatment Eventually an electrolyte-water equilibrium was established and the weight returned to the initial level

The action of chlorothiazide in diabetes insipidus seems to be specific It was compared with that of acetazolamide, dichlorphenamide, and mersalyl, but none of these increased osmolar clearance without increasing water clearance proportionally The action of chlorothiazide on osmolarity was independent of water clearance, and patients and healthy control subjects to whom chlorothiazide was administered still responded to a water-load with rapid diuresis Chlorothiazide, moreover, acted independently of vasopressin but enhanced its effect It was also effective when resistance had developed to vasopressin, and in patients with diabetes insipidus of nephrogenic origin where there was no deficiency of vasopressin

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[1] Crawford J D, Kennedy, G C., Hill, L E *New Engl J Med* 1960, 262, 737

The chlorothiazide group of drugs are unlikely to find an important place in the treatment of patients with diabetes insipidus who are satisfactorily controlled with vasopressin Besides causing depletion of potassium this group is said occasionally to cause thrombocytopenia and agranulocytosis, and possibly jaundice These drugs may, however, find a useful place in the treatment of diabetes insipidus of nephrogenic origin, and perhaps also in cases of vasopressin deficiency which have become resistant to hormone treatment

IN LODGINGS OR IN RESIDENCE?

As Prof Melville Arnott has pointed out[1] the great merit of Oxford and Cambridge lies in their collegiate life "the members of these societies go out each day to their classrooms, laboratories, and libraries but return each night to eat together, to meet their tutors, to read, and above all to talk together in hall, in common-room, and in each others' rooms" Remarking that "British universities in general are very far from providing these priceless opportunities", Professor Arnott said that in his own university of Birmingham only 12% of the full-time students were in residence, of the present total of nearly 4100, 24% live at home and 64% in lodgings All who recognise the value of the contribution that Birmingham is making and can make will be glad to hear of the appeal now launched to provide places for 1480 students and staff Given a full response, the hope is that by 1965 a third of the 5500 students will be in residence

Dr Robert Aitken, the vice-chancellor, recalls that the newer universities of the great industrial cities were at first purely civic universities, attended by students who lived in their own homes But Birmingham is now, of course, a national university as well over half its students come from other parts of the country, and over 10% of them from overseas The community at large looks to its universities for graduates showing breadth of education, knowledge of men, and ambition of a worthy kind

"Our aim", says the appeal, "is to produce men and women who are intellectually honest, unselfish in their behaviour, sensitive, competent at the tasks for which they train themselves, and genuinely interested in their fellows For this we rely traditionally, not on measures of control and indoctrination, but on the free play of human contacts and shared enterprise among the students themselves and among students and staff The great opportunities for these are in the Union, in the places where games are played, and—most important of all—in the communal life of halls of residence"

Five years ago Birmingham University bought 45 acres of open parkland within ten minutes' walk of its main Edgbaston buildings On the design of Sir Hugh Casson and Neville Conder, seven new halls are to be built on that site—some high, some low, and mostly grouped in pairs so that they can share diningrooms, kitchens and other service buildings The estimated cost of this attractive and imaginative plan is £2,588,250, of which the University Grants Committee have agreed to provide £500,000 and £1,638,250 has still to be found Contributions or inquiries should be addressed to the secretary of the University, Edgbaston, Birmingham 15

Professor Arnott, perhaps too hopefully, said that to make all the universities of Great Britain completely residential would cost £90 million It would be money well spent

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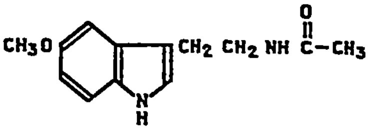
[1] Arnott, W M *Lancet*, 1959, i, 1

MELATONIN

If the Cartesian concept of the pineal gland as the seat of the soul is no longer tenable, it has been singularly difficult to replace Lerner and his colleagues[1] have isolated from bovine pineal a principle which lightens frog skin and has the power to block and reverse the darkening action of pituitary melanocyte-stimulating hormone This substance, which they have called melatonin, is the most potent lightening agent known—about 10^5 times more effective than noradrenaline and acetylcholine, which previously were the most potent of these agents that had been recognised[2] To a lesser extent such diverse compounds as 5-hydroxytryptamine, cortisol, triiodothyronine, and acetazolamide have this action, which results from the aggregation of melanin-containing granules around the nucleus of the intact melanocyte[3] Aggregation is associated with a change in the colloidal state of the cytoplasm of the cell from sol to gel, with a consequent indirect inhibitory effect on melanin formation Thus, melatonin injection will cause decreased production of melanin in hamster melanoma[2]

The pineal gland contains minute amounts of melatonin Many kilogrammes of tissue were used during its isolation, and complex extraction and counter-current distribution procedures yielded 40 µg of the compound per 100 g pineal[4] Its structure, confirmed by synthesis, proved to be N-acetyl-5-methoxytryptamine,[4] a derivative of 5-hydroxytryptamine



This compound is biologically unique Although administered 5-methoxytryptamine has been shown in the laboratory animal to be metabolised to 5-methoxyindoleacetic acid,[5] no endogenous methoxylated indole had been identified until Lerner et al[6] isolated 5-methoxyindoleacetic acid, a biologically inert substance, from bovine pineal, presumably this is a metabolite of melatonin, which was characterised soon afterwards[4] The major metabolic pathway, at least in the rat, is via 6-hydroxylation to N-acetyl-5-methoxy-6-hydroxytryptamine[7]—a detoxication mechanism which may prove of considerable interest, for there is some reason to suppose that 6-hydroxylation of an indole is associated with an increase in hallucinogenic activity[8]

In the past, methoxylation of a biologically active amine has been associated with curtailment of its function. Thus, 3-methoxylation of catechol amines is now thought to be the major physiological inactivation mechanism in man and laboratory animals[9] It is therefore intriguing to find a compound in which the substitution of a methyl group causes such pronounced potentiation of activity, which is greatest when the N-acetyl group is also present [10] Weissbach and Axelrod [11] have now identified a highly localised specific enzyme—5-hydroxyindole-0-methyltransferase—in the pineal region of the cow and monkey, which transfers a methyl group from S-adenosylmethionine to N-acetyl-5-hydroxytryptamine They achieved a twentyfold purification and showed that it was quite distinct from other methyl transferring enzymes

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Despite the apparent absence of this methyltransferase activity in sites other than the pineal, Lerner et al [12] found small amounts of a substance with the characteristics of melatonin in peripheral nerves of man, monkey, and cow This led them to speculate whether melatonin might play some part, as do most of the other known lightening agents, in the transmission of nerve impulses It may also be important in the pathogenesis of malignant melanoma or vitiligo [13] The findings in peripheral nerve are so far the only direct data on man, but human pineal gland contains very high concentrations of 5-hydroxytryptamine [14]—the melatonin precursor

Whatever the outcome of the melatonin story, it has focused the attention of biochemists on the function of the pineal gland [15]

PROGNOSIS OF THE EYE SIGNS OF GRAVES' DISEASE

A GOOD deal is now known about the biochemistry of hyperthyroidism (though its underlying cause still eludes us), but the mysterious eye changes which often accompany it remain as enigmatic as anything in medicine Sir Russell Brain [16] has usefully summarised what little is known about exophthalmos and the other eye signs of Graves' disease, and concluded that no single known factor can be the sole cause Hyperthyroidism as such cannot be primarily responsible, since exophthalmos can (and often does) advance at the very time when hyperthyroidism has been brought under control by medical or surgical means Nor can the thyroid-stimulating hormone (T S H) be the only causal factor, since blood-levels of this hormone are most consistently raised in spontaneous myxœdema, in which exophthalmos is never found Yet, though neither thyroid nor pituitary hormones are likely to act in isolation, these cannot be excluded as possible factors in the production of exophthalmos

In such an obscure condition treatment is inevitably empirical and its effects uncertain Brain recommends that hyperthyroidism, when present, should be treated, and in severe cases he recommends tarsorrhaphy, irradiation of orbit and pituitary, and surgical decompression as necessary He has not been impressed by the effects of hormonal treatment No measure applied at an early stage of progressive exophthalmos can be relied on to prevent worsening of the eyes

Although treatment is unsatisfactory, at least prognosis should be possible This demands knowledge of the long-term history of the disease, which hitherto has not been available Now, however, Hales and Rundle [17] have made a quantitative study of 104 patients with Graves' disease, whose eyes were carefully measured at the beginning and end of a fifteen-year period Three aspects of the ocular manifestations were studied separately exophthalmos, ophthalmoplegia, and lid retraction In 75 patients exophthalmometer readings were unchanged, in 24 exophthalmos had increased, and in 5 it had decreased by more than 2 mm Thus, judged by objective measurement, the actual protrusion of the eyes usually remained unchanged, but was more likely to increase than to decrease Ophthalmoplegia remained unchanged in about two-thirds of the patients, increased in 6, and decreased in 4 In this respect, the score was about "all square" Spastic retraction of the upper eyelids ("lid retraction"), on the other hand, disappeared in 60% of those who showed this sign initially, and decreased in most of the remainder Since lid retraction makes the eyes appear to protrude (even when they do not actually do so), and is responsible for a great deal of the ocular disfigurement in Graves' disease, its notable tendency to disappear with time led to a great improvement in the appearance of the patients' eyes Thus in the series as a whole most patients felt that their eyes were much better, although objective measurements of exophthalmos and ophthalmoplegia showed either no change or deterioration Hence in advising patients with the ophthalmic manifestations of Graves' disease they may justifiably be told that the appearance of the eyes will improve with time This is a great help to their morale, which usually needs all the support the physician can give

Discussing these findings, Hales and Rundle support Pochin's [18] suggestion that the factors responsible for initiating exophthalmos may be quite different from those which maintain it over long periods Pochin suggested that the initial protrusion might be permitted by weakness of the extrinsic eye muscles, this would leave a space in the orbit behind the eyeball, and a neat experiment in rabbits showed that spaces in the body are commonly filled by fat A hypothesis of this sort would account for Rundle and Pochin's [19] finding of an excess of fat in the orbit in most cases of Graves' disease, whether or not eye signs had been recognised during life

The clinical course of the eye lesions, although unpredictable in detail, usually conforms to the same general pattern A period of fairly rapid progression, lasting a few months, is followed by a very much longer period when the eye signs remain essentially static There is danger to the eyes only during the initial phase of progression, and it is then that the difficult decision has to be made whether radical measures should be applied Once the eyes have become stabilised they are no longer in danger, but may remain a source of great embarrassment to the patient Fortunately the eyes tend to look less conspicuous with the passage of time, even though objective measurement shows no decrease in the actual degree of protrusion

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SIR HENRY TIDY, consulting physician to St Thomas's Hospital, died on June 3 at the age of 82

DR G W H TOWNSEND has been elected president of the Society of Medical Officers of Health for 1960–61

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Occasional Survey

RECENT ADVANCES IN THE BIOCHEMISTRY OF PSYCHOSIS

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I SHALL here discuss some aspects of recent work on the biochemical basis of psychosis, firstly reviewing the present state of our knowledge, and secondly considering the best methods of research in the immediate future

Recent Research in Biochemical Psychiatry

Two years ago I suggested (Smythies 1958) that progress had been made because various workers had reported positive features in the metabolism and physiology of schizophrenics which differentiated them from normal people. Most of these claims have since had to be abandoned, but the evidence which was presented in support of the two main hypotheses of the ætiology of schizophrenia will now be considered in the light of the fresh evidence.

The Adrenochrome Hypothesis

In support of this hypothesis Hoffer and his associates (see Hoffer and Osmond 1959) had claimed that adrenochrome and adrenolutin are psychotomimetic agents, that adrenochrome is a normal constituent of the blood, and that schizophrenics show a decreased ability to destroy injected adrenochrome as compared to normal controls

Unfortunately the experiments which are supposed to show that these compounds are psychotomimetic are unconvincing, because, in most cases, no double-blind controls were used. Thus the results may well have been due to placebo effects, the extraordinary range of which was not fully realised at the time. Hoffer's only experiment using such controls produced negative results (see Smythies 1958) Furthermore Heath (1959a) and Pfeiffer (1959), who both tested pure adrenochrome in a dose of 50 mg, observed no effects von Taubmann and Jantz (1957) also reported that pure adrenochrome is inactive, and their further claim that some unspecified oxidation product of adrenochrome is active does not exclude the possibility of placebo effects Schwarz et al (1956) observed no psychological or behavioural effects from 75 mg of adrenochrome given intravenously, though they claim to have seen increased paroxysmal activity in depth recordings from the brains of two schizophrenic patients This evidence is unconvincing, however, as insufficient records are presented, too few subjects were tested, and no quantitative control was used

Thus whether these agents produce a condition resembling psychosis remains uncertain. The only properly designed trial so far conducted has yielded negative results, and the balance of evidence suggests that these agents are not psychotomimetic, at least when given by ordinary routes We have, of course, no means of knowing what such chemically reactive compounds might do if released by some metabolic fault in the brain, but there is as yet no evidence that this happens

Feldstein (1959) has alleged that Hoffer's claims of detecting adrenochrome in the blood and cerebrospinal fluid of normal people were based upon an unfortunate artefact in his method Thus Feldstein sees no reason to doubt the findings of Szara et al. (1958), using another method of analysis, that adrenochrome is *not* a normal constituent of blood.

Disturbed Adrenaline Metabolism in Schizophrenia

The original hypothesis, put forward by Harley-Mason (1952), was that methylation of the phenolic groups of adrenaline might somehow be concerned in the genesis of schizophrenia Five years later Axelrod (1957) discovered that o-methylation is in fact the main method of normal metabolism of adrenaline. Hence it seemed possible that disorders of this methylation process might occur in schizophrenia, and this idea led to two investigations Firstly the examination of adrenaline metabolism in schizophrenia (Resnick and Elmadjian 1956, Cohen et al 1959, Resnick et al 1958) disclosed no differences in adrenaline metabolism between schizophrenics and normal controls, either in the proportions and amounts of the various methylated metabolites or in the rates of utilisation of adrenaline or noradrenaline. Secondly, mescaline analogues were studied (see below)

Although adrenaline metabolism in the brain may be affected in psychosis (for the metabolism of injected adrenaline could well be different from that produced endogenously) there is no proof of this

Minz (1960) has reviewed the effects of schizophrenic serum on the "cortical epinephrine pressor response"

If adrenaline is placed on the exposed cerebral cortex of the rabbit, a rise of blood-pressure ensues, but, if the rabbit is pretreated with schizophrenic serum this effect is abolished or even reversed. This does not happen if the serum used is from normal people or from people under stress Even more interesting is the finding that, in animals pretreated with schizophrenic serum, the adrenaline and noradrenaline levels in the hypothalamus are raised significantly when compared with rabbits treated with normal serum The level of adrenaline was raised eightfold, and that of noradrenaline twofold. The serotonin levels were unaffected

These results will be of the greatest significance if they can be confirmed

The Serotonin Hypothesis

Recently a number of workers have been unable to show any abnormality of serotonin in psychosis

Feldstein et al. (1959) concluded from their measurement of 5-hydroxytryptamine levels in the blood and of 5-hydroxyindoleacetic acid (5-H.I.A.A.) excretion in the urine that there is no evidence, as yet, to link defects in serotonin metabolism with schizophrenia. These workers emphasised the great hour-to-hour variation in the amount of 5-H.I.A.A. in the urine and the lack of dietary controls in most studies of this kind. Brengelmann et al (1959), having previously shown (1958) that 5-hydroxytryptophan (5-H.T.P.) alleviates the psychological effects of lysergic acid diethylamide (L.S.D. 25), demonstrated that 5-H.T.P. did not alleviate the schizophrenic psychosis They thus failed to confirm the hypothesis put forward by Woolley and Shaw (1954) and a related concept by Gaddum (1954), that a naturally occurring substance resembling L.S.D. 25 is concerned in the genesis of schizophrenia

Toxic Factors in Plasma

Bergen et al (1960) using quantitative methods of evaluation have confirmed previous reports (Winter and Flataker 1958) that plasma—but not serum—from schizophrenic patients is significantly more toxic to rats and mice than is plasma from normal controls Moreover they have shown that, because the toxic factor will diffuse across a semipermeable membrane if a protein carrier is present on the other side, it must be a small molecule This finding is not specific for schizophrenia as the toxic factor is present in other types of mental illness, but the schizophrenics may be reacting abnormally to this compound, as suggested below

Melander and Martens (1959) claim to have confirmed Heath's (1959b) work with taraxein by animal experiments Their findings, although qualitative and not quantitative in design, are clear, and may be summarised thus

Taraxein, prepared from schizophrenic plasma by a modification of the original method of Heath et al. (1957) was injected intravenously into rhesus monkeys. These developed "catatonic-like symptoms" within fifteen minutes. The injection of a psychotomimetic phenothiazine called 'Kabi 888' in a small dose (2–3 mg. per kg. body-weight) produced no obvious effect. But, when Kabi 888 was given fifteen minutes after the dose of taraxein that itself produced only slight catatonia, immediate and complete loss of muscle-tone, general pilo-erection, and deep sleep were produced—effects quite unlike the ordinary taraxein reaction. The coma lasted for fifteen minutes, and then the ordinary taraxein reaction returned. During the coma the electroencephalogram showed abnormalities. Inactivated taraxein and the fraction prepared from normal plasma had no effect. When L.S.D. 25 was substituted for the taraxein the results were the same. Adrenolutin (20–25 mg. per kg. body-weight intravenously) given to monkeys had little effect by itself. But pretreatment with taraxein or L.S.D. 25 produced muscular relaxation and coma. This effect of L.S.D. 25 was shared by acetyl-L.S.D. (psychotomimetic), but not by brom-L.S.D. (not psychotomimetic).

Melander and Martens suggest that taraxein and L.S.D. 25 may enable certain drugs, injected intravenously, to act upon brain centres which are not normally accessible to them. These workers also suggest that endogenous low-molecular compounds in the blood might produce behavioural changes through the same mechanism. For instance, one could speculate that the presence of taraxein in the blood of the schizophrenic might render the brain susceptible (possibly by some action on the blood-brain barrier) to the toxic effects of the non-specific plasma constituent of low molecular weight described above. This hypothesis could easily be tested experimentally.

In this context I was able to show, by statistically evaluated quantitative methods, that adrenolutin (itself without any behavioural effect) reduces the excitatory effect of L.S.D. 25 on mice (Smythies 1959). This finding is compatible with those of Melander and Martens if we suppose that reduction of excitation and the production of flaccidity, sleep, and eventual coma are in some degree similar.

Moya et al. (1958) showed that extracts of schizophrenic urine produced a statistically significantly greater degree of hypoglycæmia in rabbits than did extracts from the urine of normal controls or other mental patients. The same extracts were also more toxic to rabbits.

These findings provide a promising basis for future work, if they can be confirmed. The chemical identification of taraxein or of the plasma fraction studied by Bergen et al. (1960) and Winter et al. (1958) would be discoveries of major importance.

Indoles in Schizophrenia

Indoles.—From time to time abnormal indoles have been reported in schizophrenic urine. But Rodnight's recent work (Rodnight and Aves 1958) probably explains why. Thus, some mentally ill subjects, particularly depressives, excrete an excess of skanonyl sulphate in the urine, but the level of excretion bears no relation to their clinical state, and it can be reduced to very low figures by giving antibiotics by mouth, without alteration in their clinical condition. Other bacterial decomposition products of tryptophan also are sometimes found. Rodnight thinks this is probably because a slower rate of intestinal peristalsis in these patients leads to increased bacterial decomposition of tryptophan in the gut, but factors affecting the intestinal flora have not been excluded.

Indole bases.—When the excretion of serotonin and tryptamine (which are the only indole bases found in urine [Rodnight 1956]) was measured in 20 schizophrenics and 20 depressives the values were normal. By the method used other indole bases could have been detected, but none was found. A special search was made for bufotenin and N-methyl tryptamines by a modification of the method capable of detecting as little as 3 mμg per ml. urine, but with negative results.

Indole acids.—Rodnight found no abnormality in the excretion of indoleacetic acid or 5-H.I.A.A. in groups of mentally ill people. Occasional subjects excreted some 5–10 times the normal amount of indoleacetic acid but this was found to be intestinal in origin.

Adenosine Triphosphate and Glucose Metabolism

Gottlieb et al. (1959) reported changes in adenosine triphosphate turnover in schizophrenics, but this was based on only 13 cases, and the results are expressed as means without standard deviations or statistical control. The raw data varied so much that their conclusions are unlikely to be valid. These same workers (Frohman et al. 1960b) have recently produced more convincing evidence, from adequately designed experiments, that schizophrenic plasma contains a factor that interferes with the control of carbohydrate metabolism.

This factor prevents the decrease in the proportion of glucose converted to ribose, by means of the hexosemonophosphate shunt, that is normally brought about by insulin. Thus the schizophrenic metabolism is relatively inflexible when tested by insulin, and it cannot change its ratio of glucose metabolised for energy to glucose metabolised for synthetic purposes under these conditions, as the normal metabolism can. Further experiments (Frohman et al. 1960a) showed that chicken red blood-cells incubated in schizophrenic plasma had a higher lactate/pyruvate ratio than had those incubated in plasma from normal controls. This suggests the presence of some inhibitor of aerobic metabolism in the plasma of schizophrenics, which may affect some phase of hydrogen transport.

Serum Cæruloplasmin Levels

Studies at the National Institutes of Health (McDonald 1958) have failed to confirm previous reports that serum-copper levels and plasma-oxidase activity are raised in schizophrenics. McDonald showed that the previous results were really due to a dietary deficiency of ascorbic acid amongst the schizophrenic population, and his results have been confirmed by Aprison and Drew (1958), Frohman et al. (1958), and Edelstein et al. (1959).

Tryptophan Metabolism

Price et al. (1959) recently reported that 6 out of a total of 19 schizophrenics metabolised *l*-tryptophan abnormally along the kynurenine pathway.

Excessive amounts of kynurenic acid, o-aminohippuric acid, acetylkynurenine, kynurenine, and hydroxykynurenine were excreted (after ingesting tryptophan) as compared to normal controls. These changes were also shown by patients with porphyria and other psychoses. Patients with neurological diseases, however, had normal tryptophan metabolism. Confirmation of these findings is eagerly awaited.

The Outlook for the Future

During the past ten years research into the biology of schizophrenia has greatly increased. But the results of all this work are a collection of negative findings that do not themselves contribute to knowledge of a positive kind, as well as a large series of contradictory reports. There is now widespread agreement (Benjamin 1958, McDonald 1958, Kety 1959) that work in this field needs new and stricter criteria of design, with much closer controls.

Better orientation of research is also needed. As McIlwain (1959) has said:

"Until the central problems of neurochemistry have been successfully tackled and we see more clearly how the nervous system utilizes its large energy supply in nervous transmission and how the brain is moulded to an animal's experience, chemical aspects of most of the neurological sciences—and above all, material approaches to nervous, mental and emotional diseases—remain as empirical as was organic chemistry before the advent of structural formulæ."

There is widespread agreement that more emphasis should now be placed on basic neurochemical and neuropharmacological research to produce a groundwork of fact upon which to base more adequate biochemical studies in the clinical field in the future. This type of research has the added advantage that, whatever the outcome, positive contributions to scientific knowledge will be made. But innumerable problems must be tackled in neurochemistry and neuropharmacology, most of which, presumably, will be irrelevant to the problems of psychiatry How, then, can we choose those that may be relevant?

One of the most promising leads in this field is the investigation of the mode of action of the psychotomimetic drugs—particularly mescaline and its near relative amphetamine. These are both closely related to physiological substances, and they produce the best simulation of the naturally occurring psychoses Clearly, if we knew the precise action of these drugs we should be able to submit the metabolism of schizophrenics to much more penetrating tests A start has been made at the Worcester Foundation (Smythies and Levy 1960) where the effect of all available analogues of mescaline have been investigated, using the Winter and Flataker (1958) rat rope-climbing test.

3 4 dimethoxyphenylethylamine has only half the activity of mescaline (3 4 5 trimethoxyphenylethylamine) Replacement of the methoxy group in the 4 position by a hydroxy group abolishes all activity where its replacement by a benzyloxy group increases activity Benington et al (1958) showed that a series of methyl-substituted phenylethylamines produced rage reactions in cats

At present very little is known about the way that mescaline works in man Block et al (1952) showed that very little mescaline ever reaches the brain, hence it may produce its effects by interfering with the metabolism of some other substance—e g, adrenaline—in the body The new metabolite of mescaline discovered by Harley-Mason et al. (1958) is a close chemical relative of vanilmandelic acid, a major metabolite of adrenaline. But the fate of 60% of mescaline when ingested by man remains unaccounted

I am most grateful to Sir Aubrey Lewis and to Dr Hudson Hoagland for their interest in this paper, and to Dr R Rodnight for the benefit of helpful discussion

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Special Articles

IRRADIATION AND MARROW TRANSPLANTATION

STUDIES IN COOPERSTOWN

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DURING the past 4 years marrow transplantation in irradiated patients, and marrow and kidney transplantation in irradiated dogs, have been studied at the Bassett Hospital in Cooperstown, New York, by a research group working with the cooperation and assistance of members of the departments of medicine, surgery, pædiatrics, radiology, and pathology[1–20] In the first year marrow

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transplantation by intravenous infusion of fresh or glycerol-frozen marrow from volunteers, cadavers, or fœtuses was assessed in leukæmic patients receiving whole-body exposure to air doses of 100–600r X-irradiation[1] The irradiation was increased to 600–1200r (6 12) of cobalt-60 gamma-ray in the 2nd year, and to 1200–2000r in the 3rd year In the last two groups exposures were continuous at 0 5–2r per minute Pilot studies were made in dogs at exposures up to 2400r at 18r per minute

Nineteen patients with acute leukæmia and one with chronic leukæmia in relapse were treated

Of these, five will not be discussed, since they were seriously infected and beyond hope Of the others, six went home improved in remissions lasting 2–6 months Eight died 1–4 weeks after irradiation, without satisfactory re-establishment of marrow function, and usually with pneumonia and capillary pulmonary hæmorrhages One went home unimproved

Of the six patients who recovered, one with chronic leukæmia in relapse had been given 450r followed by frozen cadaver marrow Evidence of temporary graft function was obtained[1] The patient had a partial remission of 6 months Two patients had autogenous return of normal marrow function within 4–5 weeks of irradiation One of these had 325r and then fresh adult marrow[6] Autogenous marrow recovery was evident after 4 weeks, and then remission lasted 6 months The second patient received 1100r followed by frozen fœtal hæmopoietic tissue (livers and spleens *) and fresh adult marrow[18] Autogenous marrow recovery was evident after 5 weeks, and remission lasted 2 months Neither patient showed evidence of survival of the attempted marrow grafts

In addition four patients with normal identical twins were irradiated with 850, 1140, 1600, and 2000r and were then given infusions of fresh marrow from the normal twin[12,19] All showed evidence of returning marrow function within 2 weeks, in contrast to the 4–5 weeks already described as necessary for evidence of autogenous return

The twin who received 2000r had a severe intestinal syndrome, but seemed well on the way to recovery at the end of the 2nd week Jaundice of undetermined ætiology appeared in the 3rd week after irradiation, and the patient died on the 20th day The peripheral blood and the bone-marrow showed evidence of partial marrow recovery The other irradiated twins with leukæmia went home feeling well and in complete remission, but their remissions lasted only for 2–3 months *One, a girl of 5 years, who was given 850r, lived for 15 months* During that period she is said to have shown no adverse effect from her radiation exposure

Finally a patient in relapse, given 400r and an infusion of his own normal marrow (stored during remission), recovered from the acute effects of irradiation and went home but without evidence of remission

Discussion

Our conclusions are that radiation is helpful in some patients with leukæmia, that autogenous marrow function after exposures of 300–1200r returns slowly, requiring 4–5 weeks for regeneration, that infusion of isologous marrow from an identical twin is followed by prompt marrow recovery even after exposures of 1600–2000r, that the intestinal syndrome that followed 2000r at 2r per minute points to this being about the limit of general radiation exposure after which survival can be made possible by marrow replacement in man

These conclusions are partly supported by studies in dogs Autogenous regeneration of marrow after dogs have been exposed to near-lethal general radiation is slow, taking 4–5 weeks[20] Marrow recovery after successful transplantation—either isologous or homologous—is brisk, taking 1–2 weeks[3,9,13] Fatal gastrointestinal complications—bloody diarrhœa and perforation—are likely after continuous exposures in excess of 1800r at 5r per minute

Evidence of successful transplantation of homologous marrow is usually seen in dogs after radiation exposures in the 800–2000r range On the other hand, experience in man at high-dose ranges has been limited Evidence of transplantation of fresh homologous marrow was seen in one patient after 1200r Another, after 1600r, showed no evidence of transplantation These patients were both leukæmic Neither survived more than 3 weeks, and the relation of their disease to their clinical course and transplantation experience is uncertain[19]

When transplantation of homologous marrow is successful in the dog, and probably also in man,[21,22] the problem of secondary disease and the graft versus host reaction, with its lymphoid and nutritional disturbances, is formidable but not necessarily overwhelming

With symptomatic treatment several dogs have survived these disturbances and regained normal health[20] One, now alive and well, shows continued evidence of graft survival a year after an exposure of 1800r Another with a successful marrow graft also received a kidney transplant from the marrow donor[15] The kidney functioned normally, and after removal of the dog's own kidneys, the transplant carried successfully the entire load of nitrogen exertion After being clinically normal for 2 months this animal fell victim to one of the intercurrent illnesses which are common during the period of secondary syndromes, and it died of thrombocytopenia and pneumonia on the 73rd day after irradiation This was 39 days after removal of its own kidneys, *and there was no evidence of nitrogen retention*

The difficulties and high mortality-rates from secondary disease in irradiated dogs successfully transplanted with homologous marrow contrast strikingly with the essentially benign clinical course of irradiated dogs that have been infused with samples of their own normal marrow kept for 2–96 hours at 4°C in tissue-culture media, or stored for longer periods in glycerol at —80° or —180°[13,17,20]

In these animals normal lymph-node histology and immune responses, as well as bone-marrow function, return rapidly[19] Probably in consequence the dogs do remarkably well both immediately after irradiation and in later months No dog in a group of fifteen exposed to 800–1500r has died of intercurrent endemic canine disease, been seriously ill, or shown after a year signs of late radiation damage After exposure to 1000r, one has recovered potency and sired a litter of four normal pups

Theoretically a similar benign course might be expected in irradiated patients treated by infusions of fœtal hæmopoietic tissue[10] To date, however, our efforts to transplant such tissue—either fresh or frozen, in man or in dog—have met with no success, for reasons that require further evaluation Our intention is to continue a cautious exploration of these and related problems of marrow and kidney transplantation[23] after high dosage of general radiation both in dogs and in selected patients

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* Kindly supplied by Dr H E M Kay of the Royal Marsden Hospital, London, S W 3

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In England Now

A Running Commentary by Peripatetic Correspondents

IN these days, when everything is known already, it is difficult for a researcher to find a worthwhile topic. Perhaps this lack of meaning in life is why there is so much preoccupation with statistical significance. At all events, statistics is in Medicine to stay, and with it has come the ubiquitous "P" Clearly, "P" is better as a servant than as a master and we must not be scared of it. The important thing is to know how an apparently hostile "P" can be made into a friend

Suppose you have discovered an association between X and Y You publish a series of cases of Y in which a surprisingly high proportion (it seems to you) are also suffering from X. The paper is entitled "X-ic Y a New Syndrome?" or "An-X-ic Non-Y-ism" or simply "X and Y in Egregious Lapsang Multips" It is not long before some fellow researcher, resting between ideas for the time being writes in caustically to say that as the association is not significant (P>0·001) he, for his part, has the gravest doubts as to the reality of the syndrome. Now, there is a riposte available to you. Having first made sure that your association is significant at a much lower probability, say, P=0·05 (and it nearly always will be) you reply as follows

> "It should be more widely understood that the figure following 'P' represents the estimated probability that the two features would be found in association as often as in fact observed, by sheer chance. When 'P' is small one can say with relative confidence that the association observed was *not* due to chance. It is merely a matter of confidence, and if Dr Q— is not prepared to take odds of 20 to 1 on, but demands the ludicrously outside odds of 1000 to 1, then all I can say is, Dr Q— has my sympathy and should take a long and restful holiday to get his nerve back."

Statistics plays an increasingly important part in the more emotionally involved fields of Medicine, and in these controversies the trick never fails

• • •

"First the little nurse with the squeaky shoes came along with a tray of things 'Just a prick, Mrs Melville,' she said. She had a go at one arm and then tried the other She went gently at it but it hurt just the same 'You've got awfully small veins, Mrs Melville,' she said, 'I'll have to ask sister to do it.' 'Well, what's all the bother about, nurse?' said the sister, and she stuck the needle in hard and pushed it about inside a bit. 'Well, would you believe it?' said the sister, 'you *have* got difficult veins, Mrs Melville! Nurse, please ring for Dr Smallweather and then prepare the instrument trolley He may have to cut down'"

• • •

"Remove the two wing nuts" it said in the car handbook, "and the panel bulbs will then be accessible" Usually, when anything goes wrong with the car I place it with all speed and a few remaining shreds of confidence in the hands of my garage man. But this was just a little green bulb on the dashboard that wouldn't light up, and so, regardless of the untimely end of Belloc's Lord Finchley, I started to tackle it myself

The first snag was that there weren't any wing nuts to be seen. I put my hand up behind the fascia, and immediately became entangled in an absolute cat's cradle of tubes and wires However, the wing nuts were there, and by treating the first one with all the delicacy which I would lavish on a gangrenous retrocæcal appendix, I managed to get it out. I had just got the second one to the end of its thread when my finger slipped, and the nut disappeared into the depths with a cascade of little clatters, rather like one of those little steel balls on a fairground machine that go round and round and round and then (appropriately enough) vanish into a hole marked "Lost".

By the time I had explored all the sharp-edged recesses behind the dashboard, dismantled the steering-column casing, and taken up the carpets, it was getting dark, so I put them all back again. I removed the instrument panel, found I still couldn't get anywhere near the bulb for the green light, replaced the panel, and fixed it with the one remaining nut. The first time I stopped the car next day the missing nut was sitting smugly on the parcel shelf

When I went humbly to the garage they said it wasn't the bulb at all, and when they had fitted a new contact-switch the green light stayed on all the time. This, they said, was something nasty to do with the big ends So now, although I don't really qualify, I shall be doing what Lord Finchley ought to have done after all.

• • •

The milk-cart rattled down the road and our Liz, a keen gardener, ran out with bucket and spade in search of treasure trove. "You can't have that, Liz—I saw it first," piped the lady next door, "and anyway it's outside my house." But Liz had beaten her to it. "A clear infringement of manorial rights," commented the lawyer across the road when he heard of the incident.

• • •

Gift-bearing Greeks are always suspect and so are gift-bearing neurotic patients One should be wary of the parcel sent to one's home or left in the consulting-room, especially in the course of treatment. It is an invariable sign of failure. Psychiatric successes are marked by the absence of gratitude either verbal or in kind.

Not all patients progressing indifferently will "buy one off" with presents, but those who do are of interest. Usually the presents are ostentatious, but cost the patient little in cash or effort. One suspects that they are prizes won at carnivals, discarded Christmas and birthday presents, the surplus of some sport or industry, or the products of a "do-it-yourself" hobby. An author will send you an autographed book, a farmer a chicken, a fisherman a cut of salmon, a confectioner a tin of sweets If by chance an expensive or well-chosen present arrives, it has come from a patient who was diagnosed as "not psychiatric" and referred to a surgical or gynæcological colleague for appropriate physical treatment. By then they have moved into an atmosphere where tangibly expressed gratitude is traditional.

Can this phenomenon be linked with the fact that no-one ever gives money to mental hospitals? Is the mind meaner than the body after all?

• • •

Simon had a little pocketmoney unspent after his seventh birthday celebrations It was suggested to him that he should open a savings account. He agreed, and accompanied by his mother presented himself at the post-office, where the clerk greeted him as an old friend.

"I want to start a Post Office book. Here's a pound."

"Put it there, Rothschild How old are you?"

"Seven."

"When were you seven?" And having asked if Simon could write and whether he understood the questions on the form, the clerk handed it over

Simon proceeded to fill it in without a smudge or blot, but my wife thought it proper to look it over before it was handed back. A good thing too, for the entry under the heading of "occupation" was certainly not legally recognisable. He had merely written "tree climbing"

• • •

If I had sat in Dunfermline town,
Drinking the blude-red wine,
If Sir Patrick had been Sir William,
Sailing a ship o' mine,

Half-owre, half-owre to Aberdour,
And fifty fathoms deep,
The Spens report and the broken ship,
Might lie at each other's feet.

Letters to the Editor

DEATHS FROM LUNG CANCER

SIR,—Dr. Hulme points out (May 28) that the ratio of male to female deaths from lung cancer in 1958 was "*considerably greater*" than the ratio in 1948 (deaths from respiratory cancer). If smoking is the cause of lung cancer and if more women are now smoking than used to, then he would expect the ratio to decrease rather than increase. "What," he asks, "have the statisticians to say?"

In reply, the statisticians would advise him not to rely upon crude death-rates at all ages. If he will compare the changes which have occurred between 1949 and 1958 at *different ages* he will find the following ratios of the male to the female death-rate (the figures for 1948 are distorted since they include mediastinal tumours):

Age in years	15–24	25–34	35–44	45–54	55–64	65–74	75 and over
1949	6·5*	2·3	4·0	8·2	8·0	5·4	3·6
1958	1·4*	2·1	3·5	6·8	9·7	9·8	6·0

* Based upon less than 30 deaths in each sex.

In short, at ages under 55 years the death-rates of women have risen nearer to those of men, at ages above 55 they have increased much less rapidly than those of men.

Statistics published by the tobacco industry show that the cigarette consumption of women was negligible before 1920 and even twenty-five years ago (1935) it was still less than 10% of the consumption of men. In 1958 it had risen to 40%. Given, on the average, a long latent period between first exposure to a respiratory carcinogen and the clinical appearance of cancer, the sex changes in mortality at different ages are not incompatible with the sex changes in smoking. We would guess that the crude sex ratio used by Dr. Hulme, and its resulting paradox, will continue to rise for some years yet.

Statisticians on both sides of the Atlantic, we may add, had not overlooked the paradox, and Dr. Hulme will find it discussed at greater length in the literature than is possible in a reasonably short letter.

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A. BRADFORD HILL
RICHARD DOLL

ANHIDROSIS AND HEATSTROKE

SIR,—The recent reports by Bannister[1] and by my good friends Sargent and Johnson in your issue of May 7[2] emphasise the complexity of anhidrosis. The sudden cessation of sweating during exposure to heat, as described by Bannister, was familiar to those of us working on climatic problems during the war,[3] and I have frequently noticed it since. This stoppage might be either general or local and was usually precipitated by some interference—e.g., if an arm was washed and dried to get a good sample of sweat at a particular time, sweating would sometimes stop on that arm. This phenomenon, which was never formally reported, suggests that when the sweating mechanism is interfered with it can easily be put out of order. Clinically it appears that anhidrosis comes on after a final insult to overworked sweat-glands. The final insult may be miliaria ("prickly heat") when it comes on slowly, or it may be from local trauma, as from drying the skin, when it comes on acutely, and undoubtedly there are many other "insults" as well. Which were operative in Bannister's and in the American cases it is impossible to say.

Sargent and Johnson report that their subjects when on a predominantly carbohydrate regime gave a diuretic response to water even when on a restricted water intake; this is not surprising, for even quite severely dehydrated subjects will "waste water" in this way.[4] What is more interesting is that subject 8T on a mixed diet providing 2000 kg calories per day not only showed a water diuresis when he was in water debt but also developed, after drinking, a transient pitting œdema. Such observations emphasise that the disorder is systemic rather than local for all its predominantly local manifestation; the diuresis and the œdema also point at least in the direction of the posterior pituitary and the adrenal cortex. Similar pointers were seen in the cases of anhidrosis described by Waterlow and myself.[5] These men were deficient in water and salt yet could not retain either. Similar cases were described by Horne and Mole,[6] but whereas their cases responded normally to antidiuretic hormone (A.D.H.) ours did not. There was similar conflicting evidence in the case of the adrenal hormones; three of four cases treated with deoxycortone responded with increased salt retention, but the fourth failed to respond. These observations, coupled with the suggestion for which there is some evidence[7] that A.D.H. partially suppresses heavy sweating, are the basis for the following working hypothesis.

Undoubtedly under the conditions in which anhidrosis occurs there will be considerable secretion of A.D.H. and of aldosterone; it is possible that with the increasing amount of A.D.H. the renal tubules become less and less responsive ("failure of the target organs") which would account for the diuresis, but meanwhile the sweat-glands would continue to be inhibited in part or in whole by A.D.H.; at the same time the adrenal cortex is fully active and it is possible that it might pass into the "state of exhaustion", partly from the thermal stress, partly from any other stress there may be—e.g., traumatic, nutritional, or infectious. The clinical picture and the response to treatment will obviously depend upon the stage at which the condition is seen. Initially the renal tubules may still give some response to A.D.H.—hence Horne and Mole's observations. The sudden outburst of sweating reported by Sargent and Johnson on rehydration might be due to the suppression of A.D.H. secretion and the consequent release of the sweat-glands from inhibition. Local changes cannot entirely be excluded; there may be blocking effects from the miliaria, and reflexes of the type described by Ferres[8] are probably also involved. There is not sufficient experimental evidence to confirm my hypothesis, but I have suggested that it does indicate the experimental and clinical observations that require to be made.[9]

Sargent and Johnson call attention to my observations that a rise in body temperature can cause the cessation of sweating, but they do not accept this as part of the ætiology of heatstroke. I have observed this falling off in sweat response (the ratio of sweat-rate to rise in rectal temperature) on many occasions in both Africans and Europeans. The falling off is exponential, and at a rectal temperature of 102°F (38.9°C) the response is so diminished that the total amount of sweat being produced is less than that produced at 100°F (37.8°C) even though the stimulus is greater. Even slight rises in temperature are paid for by a falling off in sweat response: thus men resting in heat before working sweat less than men who start work immediately with a lower initial body temperature.[10] Sargent and Johnson suggest that this could not be the basis of heatstroke because symptoms of heatstroke develop after sweating stops. What do they mean by symptoms? If they refer to coma then the answer was given by the late Eugene DuBois who pointed out that the brain can withstand body temperatures up to 105 F[11], the sweat response does not approach zero until a temperature of about this level is reached. If they refer to the rise in body temperature then I think we are back at the old question which came first, the hen or the egg?

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[1] Bannister, R. *Lancet*, 1959, ii, 313 and personal communication.
[2] Sargent, F., Johnson, R. E. *ibid.* May 7, 1960, p. 1018.
[3] Ladell, W. S. S. *Brit. med. Bull.* 1947, 5, 5.
[4] Ladell, W. S. S. *ibid.* p. 1.
[5] Ladell, W. S. S., Waterlow, J. C., Hudson, M. F. *Lancet*, 1944, ii, 491, 527.
[6] Horne, C. O., Mole, R. H. *ibid.* 1949, ii, 279.
[7] Ladell, W. S. S. *S. Afr. J. med. Sci.* 1949, 13, 145 and unpublished observations.
[8] Ferres, H. M. *J. Physiol.* 1958, 143, 39P.
[9] Ladell, W. S. S. Paper read at 6th International Congress on Tropical Medicine and Malaria, Lisbon, 1958.
[10] Ladell, W. S. S. *Trans. R. Soc. trop. Med. Hyg.* 1957, 51, 189.

Sargent and Johnson also quote me as reporting that sweating is diminished by dehydration, they do not, however, point out that I failed to find any such diminution until at least 2.5 litres of body water had been lost, which is nearly a 4% loss of body-weight, and even then the diminution was by no means pronounced.[12] It is a little difficult from their article to decide whether they accept the effect of dehydration on sweating or not, personally I doubt if it is of major significance.

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W. S. S. LADELL

BLINDNESS IN WEST AFRICA

SIR,—In an editorial two years ago[13] doubt was cast as to whether onchocerciasis was a major cause of blindness or not, three workers were concerned in the argument that it was not. The survey reported in my book demonstrates conclusively the opposite view, no matter how you may pontificate (May 28, p. 1196). If you are right then an awful lot of people are wrong in Europe, Africa, and America, where the reviews have been entirely favourable, and if the view that this disease is not responsible for very much blindness is right, it will be the first time in the history of medicine that "everybody is out of step except my Johnny". Your reply to my previous letter obscures the truth. Thus we must disagree.

Nuneham Courtenay,
Oxon.
F. C. RODGER

SELECTION OF BREAST-CANCER PATIENTS FOR ADRENALECTOMY OR HYPOPHYSECTOMY

SIR,—In their article of May 28, Dr. Bulbrook and his colleagues claim that the response to adrenalectomy and hypophysectomy for metastatic breast cancer can be predicted from determination of urinary 17-hydroxycorticosteroids (17-OHCS) and ætiocholanolone. They suggest that these estimations indicate the hormonal environment in which the tumour is growing and that this is related to the possibility of a remission after operation.

Before surgeons throughout the country start worrying their biochemical colleagues to undertake ætiocholanolone estimations, which are extremely laborious, an alternative explanation of the findings may be worth considering.

Bulbrook, Greenwood, and Hayward found that a high ratio of urinary 17-OHCS/ætiocholanolone is associated with a poor response to operation and vice versa. 17-OHCS are the urinary metabolites of hydrocortisone secreted by the adrenal cortex. In illness they are maintained at a normal level although in severe illnesses they may rise above normal. Ætiocholanolone is the main 17-ketosteroid in the urine and these are the excretory products of adrenal androgens. Adrenal cortical secretion of androgen is maintained in mild illness but is greatly reduced in chronically ill patients. The ratio 17-OHCS/ætiocholanolone is therefore high in seriously ill debilitated subjects and lower in patients whose general condition is well maintained.

An alternative explanation of the findings of Bulbrook, Greenwood, and Hayward would be that very sick patients are less likely to respond to major endocrine surgery than those whose general condition remains fairly good. It is to be hoped that the clinicians in this group will make an independent assessment of the preoperative states of these patients to examine this possibility.

London, W.1
J. D. N. NABARRO

BLOOD-GROUP DISTRIBUTION TO BE EXPECTED IN PERSONS TRISOMIC FOR THE A B O GENE

SIR,—The condition in which one chromosome in the normal complement is represented three times (trisomy) instead of twice is already known to be a cause of two congenital abnormalities in man—Klinefelter's syndrome and mongolism. Trisomy is theoretically possible for any one of the 22 pairs of autosomes in man. In addition there are four possible types of trisomy for the sex chromosomes (XXX, XXY, XYY, and YYY), making a total of 26 trisomics. Many of these (such as YYY) will be lethal at a very early intrauterine stage.

It remains possible, however, that the two known cases, mongolism and Klinefelter, are not the only viable trisomics. I have therefore thought it worth considering the possibility of a third kind of trisomic, for the chromosome carrying the blood-group gene ABO. This would produce a characteristic change in blood-group frequencies. The change would be the same if only that part of the chromosome carrying the ABO locus were trisomic.

If p, q, and r are the frequencies of the three alleles, O, A, and B in a randomly breeding population, the Hardy-Weinberg law predicts the frequencies of the various diploid genotypes. The frequencies expected for OO, OA, OB, AA, AB, and BB are given by the terms in the expansion of the expression $(p+q+r)^2$. To extend this law to the trisomic condition one merely has to substitute the expansion of $(p+q+r)^3$ for that of $(p+q+r)^2$.

The expected frequencies of the trisomic genotypes OOO, OOA, OAA, AAA, OOB, OBB, BBB, OAB, AAB, ABB, will then be p^3, $3p^2q$, $3pq^2$, q^3, $3p^2r$, $3pr^2$, r^3, $6pqr$, $3q^2r$, $3qr^2$, in that order.

Of the ten genotypes the only one which can be recognised on blood-group alone is the homozygous recessive OOO, with a frequency of p^3. The other phenotypes are represented by 3 genotypes each. This is particularly worthy of note in the case of the AB phenotype which has only 1 possible genotype in the diploid.

Let us now see how this would affect the blood-group frequencies in a given population. The normal (diploid) blood-group percentages in the Manchester region of the Blood Transfusion Service are given in the table below.

	Blood-group percentages				*Gene frequency*		
	O	A	B	AB	p	q	r
Diploid	48	41	8	3			
Trisomic	33	50	9	8	0·69	0·25	0·06

From these I have estimated p, q, and r, which in turn have been used to estimate the blood-group percentages in a trisomic population. Note the greatly reduced incidence of group O, the somewhat higher incidence of group A, and the more than doubling of group AB, which is the greatest relative change. The detailed effects of the trisomic condition will vary between populations according to the gene frequencies, but one can make the general prediction that relative to the diploid population there will be a decrease in group O and an increase in group AB.

It follows that any disease caused by trisomy for the ABO chromosome would have a blood-group distribution differing in a characteristic manner from the general population in which it arose. This is one means by which a statistical correlation between blood-group and disease could be brought about. I do not think that such an explanation has hitherto been considered.

A blood-group distribution very similar to that expected in such a trisomic population has recently been found in children's tumours arising in tissues of ectodermal origin.[1] These tumours are mostly gliomas, the rest being retinoblastomas and tumours of the sympathetic nervous system and epithelium

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[11] DuBois, E. F. Fever and the Regulation of Body Temperature. Springfield, Ill. 1948.
[12] Ladell, W. S. S. *J. Physiol.* 1955, 127, 11.
[13] *Lancet*, 1958, i, 1165.

[1] Steward, J. K. British Empire Cancer Campaign, Annual Report for 1958, pp. 533-535.

In this sample of 131 tumours, χ^2 with 3 degrees of freedom for deviation from the expectation in a diploid population was 14·91, with $P<0{\cdot}01$ The $\chi^2_{(3)}$ for deviation from the trisomic expectation was only 5·77 with $P<0{\cdot}2$ Other tumours in children (259 in number, mainly leukæmias and sarcomas) showed a normal blood-group distribution ($\chi^2_{(3)}=3{\cdot}19$, $P=0{\cdot}4$)

In a survey of many kinds of tumour such results might arise in an entirely fortuitous way That that explanation is not appropriate in this instance is shown by corroborative evidence from a much larger survey by Yates and Pearce [2] of astrocytic gliomas The situation was somewhat complicated by the restriction of the anomalous blood-group distribution to cases diagnosed since *1945*, but Steward's sample was also of recent date (1953–58) Yates and Pearce found a large excess of A over O and also an excessive number of ABs For the *309* astrocytic gliomas since *1945* the deviation from the control blood-group distribution was highly significant ($\chi^2_{(3)}=17{\cdot}9$, $P<0{\cdot}001$), whereas there was good agreement with trisomic expectation ($\chi^2_{(3)}=6{\cdot}3$, $P=0{\cdot}1$)

It was also found (Steward, personal communication) that 51 survivors of retinoblastoma (the only malignant tumour of ectodermal type with a high survival-rate) showed an excess of group A, though the χ^2 was not significant

If trisomics for any chromosome survived to birth they would be likely to have a severe disability which would appear early in life if not congenitally, like children's tumours In addition, trisomics for the ABO chromosome would have the same blood-group distribution as children with ectodermal tumours If a trisomic were fertile, he would be expected to pass the extra chromosome to half his offspring, and the condition would then be inherited like a dominant gene mutation When retinoblastoma is familial it is in fact transmitted in this way

Thus it would seem desirable to establish by direct cytological observation whether children with gliomas or other ectodermal tumours are trisomics If they should prove to be so it would be natural to conclude that the trisomic chromosome was the one carrying the ABO locus, and we should have achieved for the first time the identification of a human autosome with a genetic marker

I wish to thank Dr J K Steward and Dr P O Yates for their assistance with data and criticism of the manuscript

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A J BATEMAN

PERIPHERAL VASCULAR DISEASE TREATED BY AMNION IMPLANTATION

SIR,—In your issue of March 12 you published a further article by Mr Troensegaard-Hansen on amnion implantation I am surprised that there has been no comment in your correspondence columns on this procedure, as I have come to regard it as one of those rare gems in the catalogue of surgery of which it may truly be said that it *never* does any harm and *may* do a great deal of good

I have carried out amnion implants in some fifteen cases during the past nine years with the result that one third have been "excellent", one third "improved", and one third "no change" The cases were nearly all referred because the physician or surgeon in charge had failed to produce improvement by any other means, and the degree of severity varied between group II and group III

It has been said that because the modus operandi of the procedure is not understood it should not be taken seriously, but I, personally, believe that patients should have the chance of benefiting from any otherwise harmless treatment whether it actually works by auto-hypnosis or a general hormonic reshuffle!

I have also used amnion as a surface dressing on many occasions and find that in selected cases it is both quicker and better than Thiersch grafting I think, however, that the most important single factor in its use either superficially or by implantation is the selection and preparation of the membrane itself, and unless this is carried out strictly according to the technique formerly described by Troensegaard-Hansen then results will be disappointing I do, on the other hand, differ from him in operative technique in so far as all my implants have been carried out through a half-inch incision under local anæsthesia in outpatients

London, W 1

JOHN E BUCK

OTOTOXICITY OF NEOMYCIN AEROSOL

SIR,—I was disturbed to read Mr Fuller's report of May 7 of ototoxicity due to neomycin aerosol therapy in two children Dr Young's letter of May 28 is certainly reassuring I have used neomycin aerosol inhalations for nearly 100 patients with chronic respiratory infection in the past 3 years, and some of these have continued the treatment for more than a year The effect on the infection appears to have been less definite in many patients than that obtained with oral tetracycline treatment, but there has been no evidence as yet of ototoxicity, and I had come to regard the treatment (perhaps prematurely) as safe in this respect

I should like, however, to take this opportunity of reporting a case of severe ototoxicity following weekly intrapleural neomycin instillations (1 g dose) in a patient with a bronchopleural fistula and secondarily infected tuberculous empyema The tinnitus was first reported after the 4th week It would appear that considerable absorption of neomycin had occurred from the pleural space

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W H HELM

SOME UNCRITICISED ASSUMPTIONS IN PSYCHIATRIC THOUGHT

SIR,—In his article of March 19 Dr McConaghy helps to expose the unrecognised sadism which is the basis of the dynamic method of psychiatry

We are shown how the patient is subjected to continuous "interpretations", really nothing but criticisms of the patient's character and whole way of life, which effectively destroy his self-confidence as well as stimulate a resentment towards the therapist, which cannot be expressed without embarrassment, because the therapist seems not to be attacking the patient's character, but only helping the patient in an objective fashion The psychiatrist is shown to be a "passive-aggressive" type, unaware of his own aggressions, and unable to assume any responsibility for generating hostility in the patient, all of which, he assumes, misguidedly, is merely a reflection of unresolved childhood conflicts

Dr McConaghy's deftly written article is valuable in that it demonstrates how a therapeutic method can be, and certainly often is, made to serve destructive ends in the hands of the wrong type of person That psychoanalytic methods are *intrinsically* the expression of "passive aggression" is Dr McConaghy's main point, however, and this assertion cannot really be taken seriously All psychiatric training centres recognise as clearly as Dr McConaghy that persons with hostile or defensive characteristics should be *discouraged* from the practice of psychiatry Furthermore, it is a well-established principle of dynamic psychiatry that interpretations cannot be effective if the patient experiences them as criticisms or if they are forced upon him In fact, the ideal situation for psychotherapy is one in which, in an accepting atmosphere, for most patients a novelty, the patient becomes able to discover his own blind spots unaided

Dr McConaghy's article is entertaining to read but, unfortunately, poorly informed, and will only serve to reinforce popularly held misconceptions about the real purposes of psychiatry.

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[2] Yates, P O, Pearce, K M *Lancet*, Jan 23, 1960, p 194

Tufts University School of Medicine,
Boston, Mass.

RICHARD SCHWARTZ.

URINE OR LIQUOR AMNII?

SIR,—It is not uncommon for patients to be admitted during the antenatal period with possible premature rupture of the membranes, but following admission it is difficult to decide whether the fluid leaking is urine or liquor. It is often a simple matter to decide between the two by placing an 'Albustix' (Ames Company) on a sanitary towel which has been worn by the patient until it has become damp.

By folding the sanitary towel over and squeezing the albustix the latter will show a positive reaction for protein if the dampness is the result of liquor amnii, whereas it will give a negative reaction with urine, unless the urine contains much albumin. There is the possible error of vaginal discharge, which might also give a positive reaction for protein, but such a discharge is usually quite obvious and not difficult to distinguish between the other two conditions.

I find this test clinically useful, and it is, of course, based on the fact that the protein content of liquor amnii approximates to that in blood plasma.

General Infirmary,
Salisbury.

M. R. FELL.

PREVENTION OF TETANUS

SIR,—Dr Fulford's article and your leader in the issue of May 21 called attention to a serious problem. I have been concerned by the increase in the number of cases of serum sickness, due to A.T.S., being seen in my department. There is an increasing opinion in the profession that all patients who are given A.T.S. should be offered active immunisation six weeks later. The problem is—who should offer this immunisation? I am informed that the public-health authorities are only authorised by the Ministry of Health to use tetanus toxoid in the "triple vaccine". In practice therefore they are only able to offer protection against tetanus to infants and children. I am thus now endeavouring to arrange for immunisation to be offered at the hospital. As we give an average of seventy prophylactic A.T.S. injections a week it will be necessary to create a special clinic for the purpose.

It is essential that all those immunised should carry some indication to this effect. At present the only persons I presume to be immunised are those who have been in the Armed Forces. Parents of immunised children rarely know if the vaccine used included tetanus toxoid. At this stage it becomes apparent that this is a national problem and that it must be tackled on a national scale by the Ministry of Health. Not only should immunisation be offered to all age-groups but it is essential that a foolproof method of indicating that immunisation has been done must be devised. From my experience of diabetics in hypoglycæmic coma, the carrying of a card indicating their disability is more honoured in the breach than in the observance. I agree with your suggestion that the only reliable indication would be a small and universally accepted tattoo sign.

I hope that your leader and the discussion it has provoked on this subject will come to the notice of the Ministry of Health and stimulate appropriate action. Until this action is taken it is incumbent on all using A.T.S. to see that the patients who receive it are offered active immunisation afterwards. In this way we may begin to reduce the morbidity caused by the widespread injection of horse serum.

Casualty Department,
St. James Hospital,
London S.W.12.

DAVID CARO.

THE CAUSE OF ŒDEMA IN "COR PULMONALE"

SIR,—May I comment on the interesting suggestion of Dr Campbell and Dr Short (May 28) that œdema in "cor pulmonale" may be due to the effect of hypoventilation on renal reabsorption of sodium bicarbonate. It is the rise in pCO_2, and not the fall in pH, which is effective in promoting bicarbonate reabsorption; it might therefore be more appropriate to speak in this context of "hypercapnia", and not of "respiratory acidosis", as they do in their summary. The relief of œdema which some patients with cor pulmonale obtain with acetazolamide (whose effect is to lower both pCO_2 and pH) may support the point which I have raised—and also, of course, the general contention of their paper.

Department of Medicine,
The Royal Infirmary,
Manchester.

D. A. K. BLACK.

BACK PAIN AND HYPERÆSTHESIA

SIR,—Dr Glover (May 28) has drawn attention to a condition of the spine in a most commendable manner. As a result I hope that medical colleagues will pay more detailed attention to the spine and to the value of manipulation.

There is no doubt that he describes what the osteopaths have been talking about since the beginning of the century—the osteopathic spinal lesion. Dr G. Macdonald and Dr W. Hargrave-Wilson in their book *The Osteopathic Lesion* (1935) described the condition as an acute or chronic joint strain. Dr James Mennell in his *The Science and Art of Joint Manipulation* (1952), described it as a "joint bind". My own definition in my *Manual of Osteopathic Technique* (1959) is a "condition of impaired mobility in an intervertebral joint".

Surely we are all trying to describe and evaluate the same phenomenon. That these lesions exist there is not a shadow of doubt, but because they are difficult to demonstrate in any other way than by clinical observation, they have been missed except for a few medical men and the osteopaths and chiropractors.

The very fact that it was the unorthodox practitioners who first attempted to describe the lesion has been the cause of delay in its recognition as a clinical entity. Furthermore, terminology has confused the issue, and explanations offered by osteopaths have not been acceptable medically.

In spite of unsatisfactory theoretical considerations the practical application has not been lacking. If Dr Glover cares to glance at my book he will see detailed methods of examination which will make his tests more specific, and accurate manipulative procedures are described to correct the lesions.

By using mobility X-rays it is possible sometimes to show the restricted range of movement, and after manipulation to show the increased range, but as Dr Glover says, the size of the joints makes radiographic evidence difficult to procure and more difficult to evaluate. I must have done hundreds of mobility films to try and demonstrate the movement fault in these lesions, yet I have only one or two which will stand up to critical analysis.

It is important that these lesions are recognised early, not only to save the patient a good deal of pain but to help prevent chronicity in these joints. It is easy for symptoms to subside without restoration of movement because adjacent joints can take over their range. I am myself convinced that these minor joint lesions more often than not do persist and, with their restricted mobility, lead on to degenerative changes and in due course to disc pathology.

Let us deal with these relatively minor lesions in their early stages and treat them effectively with accurately localised manipulation and so prevent present pain and future pathology.

London, W.1.

ALAN STODDARD.

SIR,—Dr Glover deals with a sorely neglected subject. However, although agreeing wholeheartedly with the points he makes I feel bound to point out that the syndrome described is no other than the osteopathic lesion which has been recognised for many years. While this expression may be anathema to members of the profession there is no doubt that the syndrome he describes has been appreciated and treated successfully for many years by registered osteopaths and others. It seems strange therefore that such a common complaint costing so many man-hours should attract so little interest and so often receive negative and unsatisfactory treatment from the qualified doctor.

St. Thomas' Hospital,
London, S.E.1

T. M. MITCHELL-FOX

EFFECT ON THE KIDNEY OF DRUGS CONTAINING PHENACETIN

SIR,—The results reported by Dr. Harvald and his colleagues (Feb. 6) on the effect on the kidney of drugs containing phenacetin do not in my opinion substantiate the claim that 4-chloroacetanilide is chiefly responsible for the quantitative change in the urinary sediment and hence for kidney damage.

Apart from criticisms of the interpretation of the results, there are two objections to the method of comparing the three types of phenacetin. Firstly, each patient received only one type of phenacetin; to eliminate the possibility of differing patient reaction it is surely advisable to compare the three types of phenacetin in the same patients. One has only to look at the next article by Dr. Sleight in the same issue to see criticism of work where drugs were not compared in the same subjects. Secondly, the results for the control or treatment periods of all patients in each series were averaged for comparison purposes. Since the initial red blood-cell counts vary from nil to 9·4 million and the patient response is variable, this is not considered a reliable method of assessing the effect of the different treatments. If one treats the results of each patient individually there seems to be no necessity for using logarithmic values which tend to give a distorted picture.

Certain measurements of the red blood-cell count are obviously in error, such as the one of the second day of treatment of patient no. 5. Discarding five such measurements the mean values of the red-cell counts for each patient during both the control and treatment periods may be calculated. Examination of these mean values indicates a greater preponderance of increases in blood-counts of treatment periods over control periods in the case of phenacetin containing 4-chloroacetanilide than with pure phenacetin. However, if the mean values are arranged in three equal groups of patients covering initial blood-counts (millions) of (*a*) 6·0–1·2, (*b*) 1·0–0·4, and (*c*) 0·3–0·1 (see table) one finds that 6 out of 9 patients in group (*a*) were receiving pure phenacetin and 8 out of 9 patients in group (*c*) were receiving phenacetin containing 4-chloroacetanilide. Thus, each series in the investigation did not have a random allocation of patients.

MEAN VALUES OF RED CELLS (MILLIONS)

Patient	Control period	Treatment period	Increase (+) or decrease (−) with treatment
	Group (*a*)		
5	6·0	4·1	−1·9
17	5·8	3·8	−2·0
1	5·5	5·0	−0·5
2	4·2	2·7	−1·5
7	2·9	4·0	+1·1
27	2·8	4·5	+1·7
9	1·9	1·9	0
12	1·9	1·6	−0·3
4	1·2	2·9	+0·7
	Group (*b*)		
22	1·0	1·5	+0·5
3	0·9	2·2	+1·3
13	0·9	1·7	+0·8
8	0·7	1·5	−0·8
10	0·7	0·6	−0·1
14	0·5	1·3	+0·8
6	0·5	0·3	−0·2
15	0·5	0·9	−0·4
18	0·4	0·4	0
	Group (*c*)		
26	0·3	0·5	+0·2
11	0·2	0·6	+0·4
19	0·2	0·6	−0·4
21	0·2	0·5	+0·3
23	0·2	0·2	0
16	0·1	0·4	+0·3
20	0·1	0·1	0
24	0·1	0·2	−0·1
25	0·1	0·2	+0·1

Moreover, in group (*c*), 7 out of the 9 patients showed an increased count and the other 2 had unchanged counts whilst in group (*a*) 5 patients showed a decrease, 3 showed an increase, and 1 showed no change. Examination shows that the increases and decreases of mean red-cell counts with treatment within groups (*a*), (*b*), and (*c*) have a normal distribution about their mean. Thus the evidence suggests that the incidence of increase in the red-cell count with treatment is associated not with the presence of 4-chloroacetanilide in the phenacetin but with the values of the initial blood-cell count—being proportionately greater for the smaller initial values.

In the case of the white-cell counts a similar exercise shows that 7 out of 11 patients registered an increase on treatment with phenacetin, 6 out of 8 patients an increase on treatment with phenacetin containing 0·13% 4-chloroacetanilide, and 4 out of 8 patients an increase when treated with phenacetin containing 0·3% 4-chloroacetanilide. There would not appear to be a significant difference between these three series of treatments. Even the interpretation of the results by the method of Harvald et al. is not convincing. It is not sufficient to argue that "the patients in the last series (treated with phenacetin containing 0·3% 4-chloroacetanilide) had better renal functions than the first two series." No such difference exists in the red-cell counts, and if there were such a marked difference this particular series of patients should have been split between all three methods of treatment.

There would seem to be no basis therefore for ascribing changes in urinary sediment to 4-chloroacetanilide at the levels used in this investigation.

The *British Pharmacopœia* limits the 4-chloroacetanilide in phenacetin to 0·17%. Presumably careful consideration was given in fixing the limit to ensure that this content of 4-chloroacetanilide is innocuous when phenacetin is taken under any conditions except those of violent abuse.

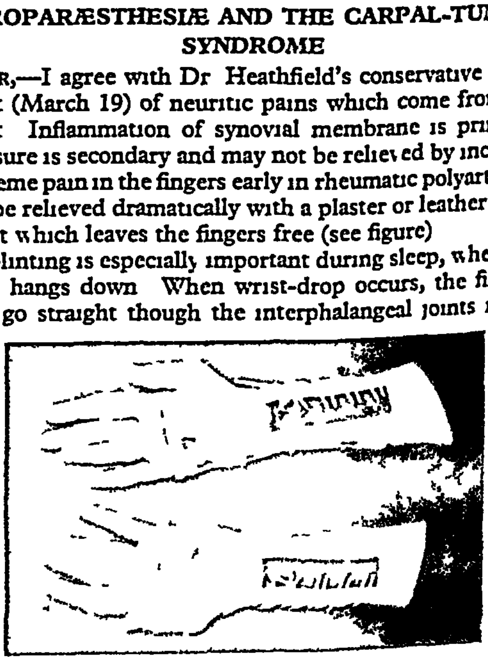
Gobowen, Shropshire

R. P. W. KUP

ACROPARÆSTHESIÆ AND THE CARPAL-TUNNEL SYNDROME

SIR,—I agree with Dr. Heathfield's conservative treatment (March 19) of neuritic pains which come from the wrist. Inflammation of synovial membrane is primary, pressure is secondary and may not be relieved by incision. Extreme pain in the fingers early in rheumatic polyarthritis can be relieved dramatically with a plaster or leather wrist splint which leaves the fingers free (see figure).

Splinting is especially important during sleep, when the hand hangs down. When wrist-drop occurs, the fingers may go straight though the interphalangeal joints never



have been arthritic. In many patients wrongly diagnosed as scleroderma, the thickened condition is secondary to arthritic wrist-drop There is usually a long history of attacks of pain and swelling of the wrist.

Institute of Rheumatology,
East Melbourne, Victoria.

MICHAEL KELLY

MOTHER'S UNION

SIR,—The letter from "The Widdicombe File" last week says that the responsibilities of the pathologist include the training of medical laboratory technicians

As a medical laboratory technician of mature years, whose feelings are also altruistic concerning the College of Pathology, I challenge this statement. The medical laboratory technician has to qualify under his own steam, to a great extent. The majority of pathologists are satisfied to get a technician using his hands, rather than his head, who will become a member of the conveyor-belt system of present-day pathological investigations

The training of medical laboratory technicians is left almost entirely to the more keen type of technicians themselves, who, with the cooperation of local education authorities, have organised courses for the benefit of those technicians who wish to prepare for the intermediate and final examinations of the I M.L T , and—let us face the facts—these senior technicians also assist greatly in training pathologists Perhaps this is a good argument in favour of "The College", so that when a junior pathologist does take up an appointment he will know at least some of the techniques required in a medical laboratory, and not have to watch the technician who because he is a decent fellow, teaches his boss his job

I heartily agree with the correspondent when he says that the worst training centres for medical laboratory technicians are the well-known medical schools, which look on these technicians as "the fetch-and-carry brigade"

I should welcome the day when the pathologist could honestly say he was responsible for the training of medical laboratory staff, as it would lessen the need for such as myself for nightly sedation, trying to organise next session's syllabus of lectures for the keen future technicians who wish to qualify in medical laboratory technology—a job that has been my lot for the past fifteen years, a job which all pathologists in the area appreciate, but none accepts as part of his responsibility (according to the Widdicombe correspondent)

St. Helens, Lancs

WILLIAM STIRRUP

HYPOGLYCÆMIA ASSOCIATED WITH SARCOMA

SIR —Like Professor Butterfield and his colleagues (March 26) we were intrigued to read of Dr Stern s hypothesis that the hypoglycæmia which developed in our patient (Jan 23) might be due to excessive aminoacid production by the tumour in a leucine-sensitive individual If our patient were leucine-sensitive it should still be possible to produce a fall in blood-sugar by performing a leucine test-meal.

The patient, who has been in good health since her operation, with no evidence of recurrence and no further hypoglycæmic episodes, kindly agreed to be admitted to hospital where a leucine test-meal was performed. 15 g (0 15 g per kg.) of L-leucine was given orally in the fasting state and blood-sugar estimations were performed at intervals over the next 90 minutes The results were as follows

Fasting	113 mg per 100 ml.	60 min	107 mg per 100 ml
30 min.	112 " "	90 min.	99 " "
45 min.	104 " "		

These figures show a slight fall probably due to the fasting state, but there is no evidence that leucine, in this dose, has had any effect on the blood-sugar The patient remained well throughout the test and had no hypoglycæmic symptoms

It seems unlikely therefore that Dr Stern's hypothesis obtains in this particular case, but it would certainly be worth while testing any similar cases in this way in the future

We are much indebted to Dr Joyce Baird, of the Department of Therapeutics, University of Edinburgh, for her help with this case.

Midwifery Department,
Foresterhill, Aberdeen.

M C MACNAUGHTON
E A F. PRIEST

"SPIRITUAL HEALERS" IN HOSPITAL

SIR,—Dr V. Cotton Cornwall, as president of the Regional Hospitals' Consultants and Specialists Association, has written to the medical press (*Lancet*, May 28) criticising the permissions granted to spiritual healers to attend the sick in hospitals (under special circumstances), and I therefore assume he has presented his strongest case against this new practice

His first argument is that the Bishop of Lichfield said that the Churches' Council of Healing does not recognise the National Federation of Spiritual Healers Does this comprise a valid objection ? The Federation is undenominational and its constitution prevents its affiliation with any other religious bodies The gift of healing can never become the prerogative of any religion and certainly not that of the Churches' Council of Healing To suggest that healers should be debarred from helping the sick, because the Churches' Council does not recognise us, is surely the weakest of arguments

Dr Cotton Cornwall next raises the point that the act of a doctor giving permission for a spiritual healer to attend his patients may lay him open to a charge of "covering " We have taken a Queen's Counsel s advice on this matter, and it is his opinion that the granting of such permission does not violate the rule of "covering" or "association", neither does it imply acceptance by the doctor of the efficacy of spiritual healing

Those are the only objections mentioned by Dr Cotton Cornwall, but he adds that members of the National Federation "should not be given special privileges, nor granted consultations with the medical staff."

We are not asking for special privileges Spiritual healing is part of our common religious belief. It is a divine act. Therefore the attendance of a spiritual healer upon a patient has the same significance as that enjoyed by ministers of religion, who visit the sick for the purpose of prayerful intercession and the laying-on of hands That is all we wish to do

We are not asking for consultations with the doctors as a right or privilege Surely there can be no harm in a doctor, if he wishes talking about a patient s condition with a healer, any more than when he discusses this with the patient's relatives or friends It seems that some doctors are trying to create difficulties when there are none, and inventing suppositionary circumstances which may never arise.

The main objection seems to be that we healers shall be giving a spiritual healing "treatment" Of course we shall, but let us get this in its right perspective. We say that a divine power or healing force is transmitted to the patient through our gift of healing There is abundant evidence to prove that this is so Surely this is what the members of the Churches' Council of Healing seek too The difference is that the healer possesses the gift of healing, and unfortunately the average parsons do not. Why deny to those patients who desire to benefit in this way the help that we can give ? Spiritual healing treatment is not in opposition to medical practice—on the contrary, it will assist the patient to respond more readily to it.

On behalf of our Federation, I thank you for the kindly references in your editorial, concerning the sincerity and integrity of our membership and recognising that we have no ulterior motives or desire to upset medical ethics You conclude by saying that when one of our members attends a patient, the other patients may think that he has the sanction of the hospital for what he does. May I suggest that we should not allow "what other patients think" to be a valid reason for denying spiritual healing to those who desire it—and there are always the screens if needed.

Guildford,
Surrey
HARRY EDWARDS
President, National Federation of Spiritual Healers

SIR,—I hope I shall be allowed to welcome your annotation of May 28 on "spiritual healers" *in the wards*, and to express some astonishment that, in this age, such a regressive step should be contemplated by some hospital management committees. Is there perhaps some disparity between the intellectual and emotional development of these, and the general body of medical opinion? It was Bernard Shaw who provocatively expressed the opinion that all conceptions were immaculate; certainly there must be few who would not hold that all healing is spiritual. However, this is not to say that, in the movements going by the names of "spiritual healing" and "faith healing", lie practical and theoretical dangers, both of naivity and esotericism. Surely the art of healing is best left in the hands of the doctors, who are fully aware of the primacy of faith and confidence, and the ministers of the great religions, with whom they share the care of the patient's well-being. If indeed the "spiritual healer" with his laying of hands is to be allowed the run of the hospitals, why not the chiropractor, the neuropath, the yogi, and the witch doctor?

London, W.1
S. CHARLES LEWSEN

SIR,—I think I can bring some reassurance to those who are concerned to the fact that a number of hospital management committees have been unwise enough to grant access to spiritual healers.

I understand that this concession is always subject to the approval of the consultant in charge of the case. On demanding whether they would allow such access to their own patients in the wards, the consultant reply I have invariably received has been, "over my dead body".

Esher, Surrey
I. S. MACDOUGALL

CHOLESTEROL DETERMINATION BY THE ZLATKIS METHOD

SIR,—Polyunsaturated fatty acids can interfere[1] with the determination of cholesterol by the procedure of Zlatkis et al.[2]

Vannini and Del Vecchio[3] compared the Zlatkis method with that of Abel et al.[4] and found that the normal discrepancy of about 7% became greater (21%) when jaundice was present (correlation coefficient between serum-bilirubin and % difference = +0·7).

In jaundice there is also an increase of biliary salts in blood which may interfere with the development of the H_2SO_4–$FeCl_3$ colour in the Zlatkis reaction.

Some biliary salt solutions become coloured if treated with H_2SO_4-$FeCl_3$. In fact

1 mg. of the Na salt of the acid	*gives an optical density of*
cholic	1·097
glycocholic	0·699
desoxycholic	0·393
taurocholic	0·155

It is not therefore advisable to use the Zlatkis method for the determination of cholesterol in serum or body fluids of jaundiced patients because of the higher readings which are accounted for not only by the high bilirubin levels but also by the increased level of bile salts in the serum or body fluids.

Istituto Ganassini,
Milan
A. DEL VECCHIO

KEROSENE POISONING

SIR,—The recent correspondence on kerosene (paraffin) poisoning prompts me to inquire whether any of your readers has had experience in treating these cases with anti-inflammatory steroids. There are several references in the literature to corticosteroid therapy being useful, and even lifesaving, in the chemical pneumonitis arising from oxides of nitrogen,[1] crude oil,[2] and aspirated stomach contents.[3] Since kerosene appears to exert a major portion of its toxic effect through such a chemical pneumonitis, steroid therapy seems worth a trial.

Haskell Laboratory for Toxicology
and Industrial Medicine,
E. I. du Pont de Nemours & Company,
Wilmington, Delaware
G. J. STOPPS

DIAGNOSIS OF POLYMYOSITIS

SIR,—The increased use of muscle biopsies in recent years has permitted the recording of many interesting observations. If, however, these findings are to be applied in the diagnosis of disease and the recognition of new disease entities, great caution must be exercised lest newly discovered changes in familiar diseases be considered sufficient justification for claiming the discovery of a new malady. Still more should we be on our guard against forcing into one group, on the basis of a single histological or group of histological appearances held in common, conditions which have been separated in the past by painstaking clinical observation. Indulgence in such uncritical reasoning is likely to discredit a valuable method of investigation and delay what might otherwise be a rapid advance in medical knowledge.

Nowhere in the field of neuromuscular disease is such caution more necessary than in regard to "polymyositis", and we must be grateful to Dr. Heathfield and Dr. Williams for bringing this matter into the open in their paper of May 28.

Under the heading of polymyositis they group 28 cases varying in age from 5 to 77 years. Some of these cases had evidence of collagen diseases (rheumatoid arthritis, lupus erythematosus), others had a carcinoma, still others resembled cases of muscular dystrophy. What then was the feature which induced Heathfield and Williams to present these cases as examples of a single disease entity? It appears to have been the presence of muscular wasting with a distribution suggesting muscular dystrophy, together with a muscle biopsy showing either focal necrosis or diffuse inflammation or both, or again, alternatively or as well, the discovery of different areas in the same muscle giving electromyograms typical of myopathies and of denervation, or of myopathic areas alone in which case there would be a strength-duration curve indicative of denervation. Unfortunately their biopsy findings are not given in detail but it is evident that in many—perhaps half—of their cases cellular infiltrations were absent or only of slight degree. In this regard it must be remembered that Dr. J. G. Greenfield and his coworkers,[4] in a relatively small series of muscle biopsies, were able to report 3 cases of *familial* proximal muscular syndromes in which there was gross leucocytic invasion and in 2 of these cases there was floccular degeneration and phagocytosis. These cases were presumably examples of muscular dystrophy and we may ask ourselves whether we are doing a service to medicine by calling such cases polymyositis on account of these histologi-

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1. Rhodes, D. N. *Biochem. J.* 1959, 71, 26.
2. Zlatkis, A., Zak, B., Boyle, A. J. *J. Lab. clin. Med.* 1953, 41, 486.
3. Vannini, P., Del Vecchio, A. *Arch. E. Maragliano*, 1956, 12, 793.
4. Abel, L., Levy, B., Brodie, F., Kendall, F. *J. biol. Chem.* 1952, 195, 357.

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1. Von V. Lachnit *Zbl. Arbeitsmed.* 1958, 8, 177.
2. Graham, J. R. *Trans. Amer. clin. climat. Ass.* 1955-56, 67.
3. Marshall, B. M., Gordon, R. A. *Canad. anæsth. Soc. J.* 1958, 5, 439.
4. Greenfield, J. G., Shy, G. M., Alvord, E. C., Berg, L. An Atlas of Muscle Pathology. Edinburgh 1957.

cal changes Dr S Nevin has also, in a recent communication to the Royal Society of Medicine, called attention to this same point.

In the remaining cases reported by Heathfield and Williams the lesions in the muscles in 3 cases were described as sarcoid-like without further details, while the remainder showed focal necrosis which was often confined *to a single fibre or part of a fibre* Even apart from the mildness of these lesions, floccular or cloudy-granular change—which would probably correspond to Heathfield and Williams' focal necrosis—was shown by Greenfield and his collaborators to be present in all their 4 cases of familial muscular dystrophy in childhood with a duration of four years or less If therefore the changes described by Heathfield and Williams can be present in indisputable cases of familial muscular dystrophy, we may ask ourselves whether some of the adult cases may not also be late muscular dystrophies or purely degenerative conditions, the cause of which remains undetected. It is true, and Greenfield admitted this that there are cases with large nodular aggregates of leucocytes but their cause is unknown and the wisdom of grouping them with conditions which have an affinity to the collagen diseases is debatable. Cases where there is a primary and indisputably inflammatory reaction in muscle without disease of other tissues would therefore seem to be much rarer than Heathfield and Williams would suggest.

Difficult though the task of interpreting muscle biopsies from this type of patient may be, surely the interpretation of electrodiagnostic data must be still less certain, since, although the electromyographer is able to detect the inability of a patient to bring motor units or parts of motor units into action, he is quite unable to determine the nature of the lesion or whether it affects the terminal motor axons or the muscle-fibre. Little wonder that the group of electrodiagnostic features put forward by Heathfield and Williams as indicative of " polymyositis " have been found by Dr P Bauwens to occur in peripheral neuritis and motor-neurone disease.[5-7] Thus we are dealing with a condition more difficult to diagnose with certainty even with the help of electrodiagnosis and muscle biopsy than was thought a few years ago But even should one feel bold enough to make this diagnosis, would one in fact be doing more than saying this is a patient with cancer or a collagen disease or neither, who has wasting of the proximal limb and trunk muscles produced by one of a number of different mechanisms as yet unknown to us?

Walton and Adams [8] in their book on polymyositis report 40 cases of this " disease " which represented their personal experience (which included access to the files of the Massachusetts General Hospital) over a period of more than twenty years 6 of these cases were of carcinomatous myopathy, 20 showed evidence of collagen disease, and 14 formed a heterogenous group of great interest but of such variability in age of onset and symptomatology as to make one doubt whether even in this one group the patients were suffering from the same disease. These authors performed an important service in showing that patients with the same histological changes in the muscles could suffer from such various diseases, and we would do well to remember that the repertoire of histologically demonstrable reactions of muscle is small. To recognise that carcinoma may be associated with changes in the muscle resembling those seen in muscular dystrophy and in collagen disease constitutes an advance, but to imply that these patients are all suffering from one disease—polymyositis—is in my view a retrograde step

While not denying that there are many diseases affecting muscles rather than their nerves, and which differ in their natural history from the classical muscular dystrophies, would it not be better at this stage to follow Greenfield and report only what we see and not introduce a new name which as often before will form a favourite but quite misleading diagnosis?

The Midland Centre for Neurosurgery,
Holly Lane, Smethwick.

A. L. WOOLF.

RECTAL EXAMINATION

SIR,—Time and again in your journal attention has been drawn to the valuable aid given to diagnosis by digital examinations of the rectum, in fact, I believe Osler stated that a consultant physician was one who did this examination when other physicians had failed to do it.

I feel the examination is often neglected in people's homes because of the difficulty in disposing of a rubber glove. For this reason I should like to draw attention to a plastic disposable finger-stall with a hand-guard made by Down Brothers This finger-stall is always clean and the hand is adequately guarded—and it is disposable. All of which can be got for a trifling cost.

New Cross Hospital,
Wolverhampton, Staffs.

KENNETH HAZELL

HISTORY OF IPSWICH MEDICINE

Mrs I HEWITT, librarian of the Ipswich Medical Library writes

"The Ipswich Medical Library has decided to set up a historical section of records appertaining to the origin and growth of medicine in Ipswich and District, involving hospital practice, general practice, and public-health practice.

The historical section hopes to include documents books, photographs, and instruments Any help your readers can give would be appreciated and should be sent to the Ipswich Medical Library, Anglesea Road Wing, Ipswich and East Suffolk Hospital."

GIFFEN HOUSE, ROYAL MEDICAL BENEVOLENT FUND

Commander J. G HUNT, secretary of the Royal Medical Benevolent Fund, writes

"May I draw the attention of the medical profession to Giffen House, 15, St. Simon's Avenue, Putney, which was opened in 1959 to provide five rent-and-rates-free unfurnished flats for retired married doctors with restricted incomes

The house is situated in a quiet neighbourhood, not far from shops and public transport, and has a pleasant garden. The flats, of two rooms, kitchen and bathroom, with electric heating, are spacious and entirely self-contained. The only charge is a contribution to the maintenance of the property of £25 yearly

We have two flats unoccupied. Applications and enquiries from retired married doctors are invited and should be addressed to The Secretary, Royal Medical Benevolent Fund, 37, St. George's Road, Wimbledon, S W 19"

Public Health

Clean Air

BY the end of last year, 510 smoke-control orders were in operation or preparation (compared with 226 at the end of 1958)[1] The orders covered 105,000 acres and 600,000 premises in England and Wales Most of them related to " black areas " Greater London had 140 orders, South-east Lancashire 84, the West Riding of Yorkshire 82, and the West Midlands 60

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[5] Bauwens, P *Proc R Soc Med* 1954, 47, 918

[6] Bauwens P *ibid* 1955, 48, 194

[7] Bauwens, P *Amer J phys Med* 1959, 38, 109

[8] Walton, J N., Adams, R. D Polymyositis Edinburgh, 1958

[1] Report of the Ministry of Housing and Local Government, 1959 H.M. Stationery Office Cmnd. 1027 Pp 229 10s. 6d

Parliament

Flame-resistant Materials

ON the adjournment on May 30 Mr GEORGE CRADDOCK recalled that each year over 1500 people died and over 1 million were injured by fire. More than half of the hospital cases were due to accidents caused by wearing inflammable clothing, and most of the victims were children. A new and improved flame-resistant finish for materials had been developed by Proban Ltd. and could now be applied to cotton and winceyette. Yet mothers still had difficulty in obtaining non-inflammable material for nightdresses for their children. He asked the Minister to give Government backing to the labelling of safe materials, to enable shops which sell them to put up appropriate notices, and to arrange for the Board of Trade to help in advertising campaigns and to see that the testing of these materials was kept up to standard.

In his reply Mr JOHN ROGERS, parliamentary secretary to the Board of Trade, said that the Molony Committee[1] in their interim report, which had now been presented to Parliament, had considered the suggestion that the use of flame-resistant fabrics should be a statutory requirement, at any rate in certain forms of cloth, such as children's nightwear. But they had been unable to recommend compulsion at this stage. To his knowledge, three processes could render certain fabrics flame-resistant. Large sums of money had been spent on their development. Materials treated by these processes had been handled by retailers but the public response was bitterly disappointing—"negligible" was the only word to describe it. Why was this so? They had been told that it was because the treatment made the cloth hard or harsh to the touch and because the treated fabrics were more expensive. It was claimed that a further technical development in at least one of the processes had now eliminated the adverse effect on handle. If so, there remained only the question of price. The processes added to the cost of, say, a nightgown for a small child about the price of 20 cigarettes. Was 4*s* too much for safety?

There had been suggestions that taxpayers' money should be spent on an advertising campaign to persuade people to ask for fabrics which were either naturally flame-resistant or had been rendered so by one of the commercial processes. He did not think that this was a right purpose for the spending of the taxpayers' money, but he was attracted by the idea of a special campaign warning mothers of the dangers and apprising them of the availability of these new finishes and possibly new fibres which came on to the market. All were agreed that some educative and sustained publicity would be valuable. The only difference between them was whether this should be undertaken by the taxpayer or by those who ultimately hoped to profit by the exercise—namely, the makers of the fibres, the makers-up of the garments, and the distributors who sold the children's nightwear in the shops. For such a campaign to be effective it was essential that these garments should be stocked widely, and he would like to see the big retail stores give a lead by stocking flame-proof pyjamas and nightgowns. He believed that the stores and the makers-up should stress this feature in their advertisements continuously. We must hammer it home until it was accepted by the public that these fabrics were available in most of the shops throughout the length and breadth of the country. Nevertheless, he still thought that it was not something on which the Government ought to spend money.

Royal Assent

The Population (Statistics) Bill, the Radioactive Substances Bill, and the Royal College of Physicians of London Bill received the Royal Assent on June 2.

QUESTION TIME

Medical Auxiliaries

Lord FRASER OF LONSDALE asked the Government whether, having regard to the general satisfaction felt at the result of the Royal Commission on Doctors' Remuneration and the Government implementation of its recommendations, and having regard also to the new importance now being attached to medical auxiliaries, as evidenced by the passage through Parliament of the Professions Supplementary to Medicine Bill, they will now set up a Royal Commission or other appropriate body to inquire into the salaries and conditions of work of the professional persons covered by this Bill.—Viscount HAILSHAM replied: In the view of Her Majesty's Government, the special circumstances which led to the decision to set up the Royal Commission on Doctors' and Dentists' Remuneration have no application to the professions covered by the Professions Supplementary to Medicine Bill. The remuneration and conditions of service of members of the professions employed in the National Health Service are negotiated by the National Health Service Professional and Technical Whitley Councils A and B, and the Government consider that the normal opportunities for negotiation provided by this machinery are fully adequate for their purpose.

Lord FRASER OF LONSDALE: With respect, does not this look like one law for the doctors and another law for the supplementary workers, without whom the doctors would be powerless to do their jobs? Does my noble friend know that the supplementary workers are not satisfied with the Whitley Council, and will he reconsider the answer which he has given?—Lord TAYLOR: Before the noble Viscount replies, may I ask whether he is not aware that there are Whitley Councils for the doctors, but that fact did not stop the setting up of a Royal Commission for them? These professions are in an infinitely worse financial position than the doctors, and, while not subscribing completely to the noble Lord's observations about doctors and the supplementary professions, I would agree that the value of their work is very great and their remuneration very poor.—Viscount HAILSHAM: I cannot for an instant accept the proposition that because a Royal Commission is set up to discuss the remuneration in one profession, in all other cases of wage negotiations it is to be treated as a slight on the employees if a Royal Commission is not set up in that profession, too. That seems to me to be the wrong way of approaching the matter, and it would, in fact, be a counsel of despair in all wage negotiations. The circumstances which led to the appointment of the Royal Commission for doctors and dentists were that a fundamental disagreement had developed between the Government and the two professions about the basis on which the professions' remuneration in the health service ought to be determined. Complex questions had arisen, such as the precise meaning of what had been implied by Government acceptance in principle of the three Spens reports. According to the Royal Commission, the disputes which arose did "nothing to promote the smooth working of the National Health Service". I should hardly think that a comparable situation had arisen in relation to the seven supplementary professions. Since October, 1959, the National Health Service salaries and sessional fees of six of the seven professions covered by the Bill have been increased by agreements freely arrived at on the appropriate Whitley Council. The salaries of the remaining class, the radiographers, were determined, in default of agreement, by an award of the Industrial Court, effective from Feb. 1, 1959. In all cases the increases were more than would have been justified by increases in the cost of living alone, and in some cases were very considerable.

Lord STONHAM: I am sure the noble and learned Viscount is absolutely right in rejecting the suggestion of a Royal Commission, but is he aware that these people are disgracefully underpaid, a fact which creates great difficulties in the running of hospitals? Whilst conceding all he says about the Whitley Councils, I would ask him whether he would have a word with his right honourable friend to see if something could be done. After all, the last increase for radiographers was in February last year, and they are surely entitled now to a further increase.—Viscount HAILSHAM: I think I must assume in all wage negotiations that the ordinary negotiating machinery should be used first.

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[1] *Consumer Protection: interim report.* Cmnd. 1011. H.M. Stationery Office, 1960. 1*s*.

Obituary

JOHN FARQUHAR FULTON

O.B.E. (Hon.), M.D , B S Harvard, M.A., D.Phil., D Sc., D Litt Oxon., F.R.C.P

Prof John Fulton, neurophysiologist and historian and bibliographer of medicine and science, died at his home in New Haven, Connecticut, on May 29 at the age of 60

He was the son of J F Fulton, an ophthalmologist of St Paul, Minnesota He graduated B.S at Harvard University in 1921 and went as a Rhodes scholar to Magdalen College, Oxford, where he became a university demonstrator in physiology under Sherrington. He was befriended by Lady Osler and was given the run of Osler's library where the great *Bibliotheca Osleriana* was in the making

In 1927 he returned to Harvard to take the M.D degree and worked as an associate in neurosurgery under Harvey Cushing at the Peter Bent Brigham Hospital in Boston Election to a fellowship at Magdalen brought him back to Oxford in 1928 to continue his neurophysiological researches in Sherrington's laboratory until he was appointed Sterling professor of physiology at Yale University in 1931

His capacity for hard work soon placed his department in the forefront of neurophysiological research laboratories, and his infectiously enthusiastic and endearing personality attracted students and workers from all over the world Important papers were published by him and his associates in a steady stream

His paper with C F Jacobsen on the functions of the frontal lobes (1937), his William Withering lectures at Birmingham University (1948), and his Sherrington lectures at Liverpool (1952) helped to provide a neuroanatomical rationale for leucotomy operations, while his *Physiology of the Nervous System* (1938) has become a standard text Other important contributions were his monographs on *Muscular contraction and the reflex control of movement* (1926) dating from his Oxford days, *The sign of Babinski a study of the evolution of cortical dominance in primates* (1932), and papers on human and comparative studies of cortical and autonomic nervous system function and localisation.

Despite this great scientific output, Fulton managed to carry on his humanistic studies in the history and bibliography of medicine and science.

As early as 1930 in his *Selected Readings in the History of Physiology* he showed an extraordinary grasp of important trends, experiments, and discoveries in the development of knowledge of vital processes In 1932 his *Bibliography of the Honourable Robert Boyle* was published by the Oxford Bibliographical Society, and he was correcting page proofs for a new edition when he died It remains the classic example of that most useful art of scientific bibliography which not only lists books and other writings but also analyses their contents and evaluates their contribution and place in the historical scene. His bibliography of Richard Lower and John Mayow was written on the same lines His biography of *Harvey Cushing* (1946) was a work of poetry and art worthy to take its place with Cushing's own *Life of Sir William Osler* (1924)

During the late war Fulton turned his energies to aviation medicine, and his work for the war effort in this country was recognised by his appointment as honorary O.B.E He also organised the evacuation of a large party of English children to the United States, and he and his wife generously undertook the education and maintenance of some.

In 1951 Fulton left the chair of physiology at Yale and became Sterling professor of the history of medicine in the same university His department rapidly achieved world status, and his editorship of the *Journal of the History of Medicine and Allied Sciences* was also successful Though he never forsook his neurophysiological interests and remained editor of the *Journal of Neurophysiology*, he gave more and more time to historical and bibliographical subjects, and he had the satisfaction of seeing the department he created, and the great Harvey Cushing-Arnold Klebs-John Fulton collection of historical medical and scientific books, incorporated within Yale University as the most important centre of medical and scientific history in the world.

Fulton travelled often and widely, all over the world, and wherever he went he was known and loved. He received many lectureships and honorary degrees, including awards in no fewer than eighteen countries He valued above all else the D.LITT which he received at Oxford in 1957 He was elected F.R.C.P under the special bye-laws, and he was an honorary member of the historical section of the Royal Society of Medicine and an original member of the Osler Club of London

The following tribute comes from a medical librarian

" John Fulton was a life-enhancer, the world will be a less enjoyable place for the innumerable friends he has left His incessant activity, though it cost him his life, never seemed to weary his spirit He would go to the ends of the earth to meet a friend, to watch new work, or to seek a rare book. He loved the Renaissance with its gusto for both the highest and the merriest pleasures, and shared its urge towards new discoveries He was a ransacker of book-shops but a generous friend to many libraries, not only the munificent co-founder of the splendid medical-historical collection at Yale Last year he put on record his conviction that the recent growth of the medical library is ' challenging evidence of its importance in education and research '. Many, indeed most, medical librarians in America, Canada, and Britain can hardly count how much they owe to John's unfailing encouragement of their efforts "

R. A. H writes

" Fulton's was a manysided personality with apparently contrary characteristics making up a harmonious whole. To name only a few he had an inexhaustible capacity for work and could relax and enjoy himself with equal vigour, he was as enthusiastic over a book on a shelf as over good food at a banquet, he was an untiring collector and yet so generous that libraries in many lands have reason to be grateful to him for gifts of rare books which he felt properly belonged to their collections, he was a public-spirited individualist not without a lovable streak of vanity who could devote himself equally to causes and persons, his views were carefully arrived at and firmly held, yet he was quick to accept and foster new ideas, he had the capacity to abstract himself completely when absorbed but was always ready to meet and exchange ideas with kindred minds, for him to commune with great figures of the past like William Harvey and Kenelm Digby was as lively as gossip about his own contemporaries, which he also enjoyed He regarded all workers in the advancement of knowledge—whether scientific, historical, or bibliographical—as belonging to a club of which he was proud to be a member In it he included the men of the past (hence his devotion to history) as well as the generation to come (hence his active and unstinting support for the young and aspiring) *He caught at* Oxford the scientific spirit of Sherrington and the humanistic tradition of Osler to whose library his widow gave him the key

Royal College of Physicians of Ireland

At a meeting on June 3 the following were admitted to the fellowship

J D Whiteside, Patricia M Alston, Joan M Mullaney

M B Levine was admitted to the membership and the following to the licence and membership

Joseph Alvey, Phelim Donnelly, J B Hourihane, C F McCarthy

Royal College of Surgeons in Ireland

On June 1 the fellowship was conferred on Ratan Lal Agarwal

Faculty of Anæsthetists—The fellowship of the faculty has been awarded to the following

T J Gilmartin, dean, V O McCormick, vice-dean, P Drury Byrne, P Nagle, S Kenny, P Murray, J Woodcock, R Davys, J Dundee, S Love, K Bayne, W Bingham, S Bose, J Boyd, J D Bourke, G J C Brittain, A B Bull, F M Bryn, D G Coleman, W S Davis, J B Glynn, T F Heavey, J C Hewitt, A H Kasasian, O V S Kok, M V Lemon, B Lyne, P R Mersham, M Murphy, J MacAuley, M O Connor, S D Oliver, Lady Read, D L Scott, R W Shaw, M A Woods, Z Lett

The inaugural scientific meeting, which will take the form of a symposium on levels of anæsthesia, will be held in the college, St Stephen's Green, Dublin, on Saturday, July 9, at 10 A M Further particulars may be had from the registrar of the college

University College of Sierra Leone

Dr Davidson Nicol, senior pathologist to the Government of Sierra Leone, has been appointed principal of the University College of Sierra Leone (Fourah Bay College)

He was born in Sierra Leone in 1924 and he was educated in West Africa, the University of Cambridge, and the London Hospital He took first-class honours in part 2 of the natural sciences tripos in 1947, and qualified three years later After holding resident appointments and a research assistantship in the department of physiology at the London Hospital, he became lecturer in physiology and biochemistry at Ibadan University College in Nigeria He returned to Cambridge in 1954 with a Beit fellowship to work with Prof F G Young and Dr Fred Sanger in the department of biochemistry He proceeded to the degrees of M D in 1956 and PH D in 1958 and was elected a fellow of Christ's College He left Cambridge last year to join the Sierra Leone medical services He is a member of the West African Medical Research Council and has published work on tropical malnutrition, the structure and biological activity of insulin peptides, and the tropical anæmias

Society of Apothecaries of London

At recent examinations the following were successful

M M S A—S R Hewitt, J D H Mahoney, A I Qureshi, T A Rahman

L M S S A—A K Trounson, E Aihie, L B Oshin, B R Collier, J G Fairer, C G D Joseph, A B Chinnappa, O Grundstrom, R Handley, N C MacCallum, N Sabokbar, L A B Murray, G Dickens, E M W Haire, I F Ayad, W G S Russell, J L Lane, Y P Lee, J K C Chung

Postgraduate Medical School of London

A symposium for consultants on the diagnosis and treatment of chronic forms of arthritis will be held on Sept 22 and 23 at the school, Ducane Road, W 12 Further particulars will be found in our advertisement columns

Rehabilitation From Incapacity to Capacity

The British Council for Rehabilitation of the Disabled will hold a course and conference on this subject in Dublin, from July 12 to 14 Further particulars may be had from the council, Tavistock House South, London, W C 1

Institute of Child Health, London

Donations to the institute's building appeal fund now total £100,000 towards the target of £400,000 The Mathilda Marks Kennedy Trust have given £40,000 to provide the main lecture theatre in the new building

Wellcome Trust

The Wellcome Trustees have made a grant of £50,000 (about $140,000) to the Massachusetts General Hospital, Boston, for the establishment of a Henry S Wellcome research chair in medical science The professor will be chosen by a special committee of the Massachusetts General Hospital, Harvard University, and the Massachusetts Institute of Technology, from a number of workers who have already achieved a high scientific reputation for their researches The appointment will be made for ten years

Royal Dental Hospital, London

Mr Warwick James, F R C S, has given £22,000 of 2½% Consolidated Stock to the School of Dental Surgery to endow a fund for research on dental anatomy

British Medical Association

The Association is offering essay prizes for medical students, provisionally registered practitioners, members engaged in th practice of occupational health, and general practitioners Awards are also to be made of the Middlemore and Katherine Bishop Harman prizes Further particulars may be had from the secretary of the Association, Tavistock Square, London, W C 1

Birmingham's First Health Centre

On May 17 Mr Derek Walker-Smith, the Minister of Health, opened a health centre in a new housing scheme at Nechells

The centre, which is on the ground floor of a seven-storey block of flats, has six surgeries for general practitioners, a dental suite, a maternity and child-welfare centre, and a staff common room A reception office relieves the doctors of much of their clerical work The office for the district home-help service is also in the centre, and a midwife and pupil occupy one of the flats above the centre A resident caretaker takes messages after surgery hours The centre is intended to serve 45,500 people and will cost £12,850 a year to run

Eclampsia and Pre-eclampsia in Pregnancy

The International Society of Geographical Pathology is holding an international conference on this subject at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W C 2, from June 28 to 30

The president of the conference will be Prof J H Dible and th speakers will include Dr Ian MacGillivray, Dr Richard Doll, Prof J C McClure Browne, Sir Dugald Baird, Dr A D T Govan, Dr H B Goodall, Dr A E Claireaux, Dr A I Klopper, D M J R Dawkins, Dr J V Wigglesworth, Dr D A Davey, Mr M Mahran, Dr Edda Hanington, Dr H B Perry, Dr Heather J Shelley, Prof R J Kellar, Dr H G Kohler, Dr H B Goodall, Dr W E Miall, and Dr A L Cochrane

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Dr L Guttmann, director of the National Spinal Injuries Centre, Stoke Mandeville Hospital, Aylesbury, has received the 1960 international prize of the Spanish Association for Invalids and Handicapped

The John Holt medal awarded to Sir Samuel Manuwa by th Liverpool School of Tropical Medicine was presented to him a Government House, Lagos, by the Governor-General of Nigeria, who read a congratulatory letter to Sir Samuel from the Duke of Edinburgh, patron of the school

The Postgraduate Medical School heart surgery team (Mr W P Cleland, Dr D G Melrose, Mr H H Bentall, and Dr A Holman) are carrying out a demonstration series of intracardiac surgical procedures, with the use of the extracorporeal circulation, in Helsinki, Finland

The Anglo-German Medical Society is holding a symposium on medical education, on July 30 and 31, in Stuttgart Further particulars may be had from the hon secretary of the society, c/o department of chemical pathology, St Mary's Hospital, London, W 2

Appointments

Blyth, R A, M B Lpool senior M O (mental health), Cheshire

Gore, Elizabeth, M D, D OBST, D P M consultant in child psychiatry Harrogate child-guidance clinic of the West Riding Education Committee

Kamaluddin, S M, M B Calcutta, D O assistant ophthalmologist, Barnsley area hospitals

Le Quesne, L P, D M Oxon, F R C S assistant consultant surgeon, Middlesex Hospital London

Turner Warwick, R T, D M, B SC Oxon, F R C S, M R C P assistant consultant surgeon, Middlesex Hospital, London

South-Western Regional Hospital Board

Foster, G S, M D Lond, M R C O G consultant obstetrician and gynæcologist, Weston-super-Mare group of hospitals

Gordon, D T, M B Aberd, D P H S H M O in infectious diseases [illegible] Isolation Hospital Plymouth

Pryer, D L, M B Lond, F F A R C S consultant anæsthetist, Torbay area hospitals

Roddie, R K, M B Belf, F R C S consultant E N T surgeon, Bristol clinical area hospitals

Soltau, D H K, M B Cantab, F R C S, M R C O G consultant obstetrician and gynæcologist, North Gloucestershire clinical area hospitals

Thomson, D S, M B Durh, F R C S E, D O M S consultant ophthalmic surgeon, North Gloucestershire clinical area hospitals

The Lancet · Saturday 18 June 1960

THE FEMALE PROSTATE *

BLADDER-NECK OBSTRUCTION IN WOMEN

THOMAS MOORE
M.D , M.S Durh., F.R.C.S
CONSULTANT SURGEON, UNITED MANCHESTER HOSPITALS

ALTHOUGH hardly recognised in this country, bladder-neck obstruction in women is a very real condition which is not so very uncommon. In a previous communication I described eleven cases (Moore 1952) This paper is based upon thirty-three of the cases encountered since 1948 Not infrequently the wife of one of my prostatic patients has said to me, " I am sure I have the same trouble myself, I have just the same symptoms " Sometimes this diagnosis has been correct In one family I have removed a grandfather's prostate, his son's, and his daughter-in-law's, all with equally good results!

The bladder neck is the junction between the bladder and the urethra. The circular muscle of the latter normally holds it closed, and only when this junction is open can micturition occur Many now regard the urethra and the bladder in the female, and the bladder and the posterior urethra in the male, as one viscus They are certainly intimately related in function, and minor changes at the junction between them can lead to gross interference with micturition. It is generally known that the detrusor muscle of the bladder is continued into the proximal urethra. There is also a large body of muscle posteriorly under the trigone, partly derived from ureteric muscle which enters into the posterior urethra. When micturition occurs, contraction of the detrusor muscle leads to shortening of the urethra and pulling open of the sphincter muscle at the bladder neck (fig 1) This mechanism can be demonstrated by the study of cysto-urethrograms taken at different phases of micturition, by cineradiography using the image intensifier, and also by endoscopy itself From my own observations I have no doubt that the female bladder neck usually opens more easily than in the male, and opens in the entire circumference of the orifice whereas in the male it is mostly the posterior quadrant which moves This difference in function of the bladder neck in the two sexes is associated with the more rigid nature of the structures round the bladder neck in the male and explains the higher incidence of bladder-neck obstruction in that sex.

Any thickening or rigidity of the bladder neck in the female will make it more difficult for the muscles of the bladder to pull it open. Obstruction is then present The factors which can be responsible for this loss of flexibility can be inflammatory, consisting of œdema, cellular infiltration, and fibrous-tissue formation, glandular hyperplasia, internal-sphincter hypertrophy, or, in rare cases, neoplastic change.

The female urethra is surrounded by very many glands (fig 2) Many believe that these represent the homologue of the prostate in the male. Several workers, Folsom (1931) and Young (1940) particularly, have been impressed by the similarity of the tissue excised from the bladder neck in the female to that of the prostate in the male, and have regarded the condition as the female prostate There is no doubt that the prostate is under hormonal control and it may well be that the female urethral glands are too Young (1940) described a case of adrenal virilism in the female in which hypertrophy of these glands was such that to the naked eye the structure below the bladder neck

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* Based upon a lecture given to the section of surgery of the Manchester Medical Society on Feb 10, 1959

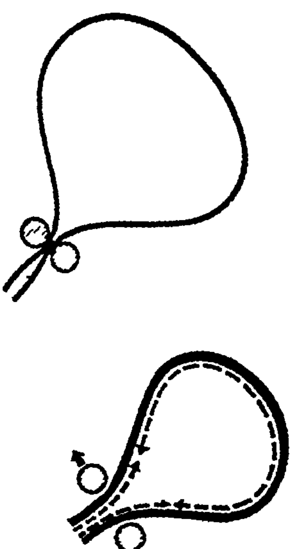

Fig 1—Schematic representation showing how contraction of the detrusor muscle of the bladder causes shortening of the urethra and opening of the bladder neck.

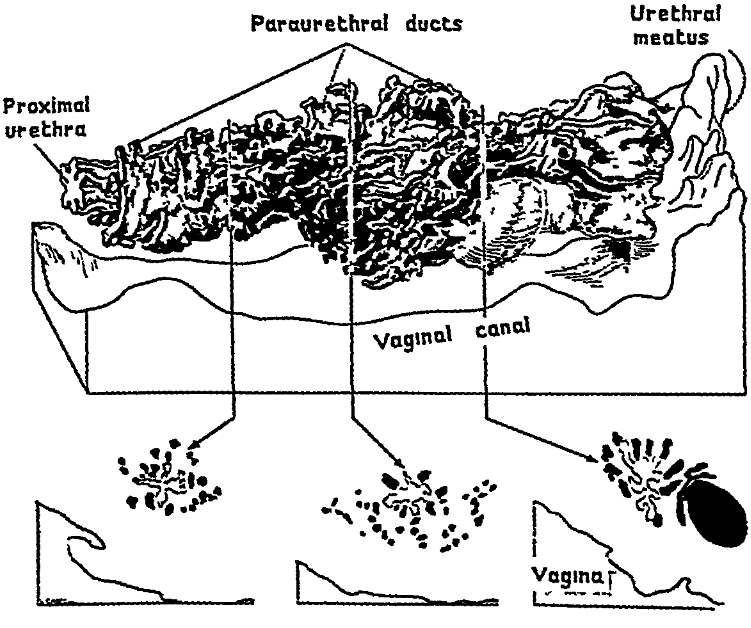

Fig 2—Wax model representation of the urethra showing paraurethral glands. (Huffman, J W A.M.A Arch Surg 1951, 62, 615.) Reproduced by kind permission of the author and publishers.

resembled the prostate The condition is certainly commonest in the prostatic age-group In my cases, however, the tissue excised from the bladder neck has not really simulated a true prostatic adenoma The common findings have been squamous metaplasia of the epithelial lining of the bladder neck and infiltration with inflammatory cells, œdema, or fibrosis In one case there appeared to be hypertrophy of the internal sphincter All this patient's reactions were slow and we postulated there was some neuromuscular dysfunction at the bladder neck leading to hypertrophy of the internal sphincter Obstruction at the bladder neck causes hypertrophy of the detrusor muscle which may still be able to empty the bladder completely Then, as decompensation of bladder function occurs, increasing amounts of residual urine remain after each micturition Finally chronic retention ensues and the ureters become dilated and associated with hydronephrosis and renal insufficiency In addition the urinary stagnation encourages infection with all the associated dire possibilities

Relation of Bladder-neck Obstruction to Cystocele

As it is, unfortunately, still traditional for urinary symptoms in the female to lead to a gynæcological consultation, I must discuss the relation of bladder-neck obstruction to cystocele

In my view cystocele and uterine prolapse per se are not the cause of urinary difficulty, nor is there any reason why they should be The bladder is a powerful muscular organ which will contract even when isolated from the body Recently I encountered a patient with an extreme degree of uterine prolapse and cystocele without any urinary symptoms of any kind

As cystocele is a comparatively common condition it is often operated upon in the belief that it is the cause of the urinary symptoms In my experience these are rarely, if ever, cured thereby Colporrhaphy must be associated with much postoperative fibrosis That which occurs round the bladder neck may render it difficult to open and cause urinary obstruction Thus the urinary symptoms whatever their cause may be made worse When, as sometimes happens, an undiagnosed bladder-neck obstruction was present originally, the final condition is much worse than the first, residual urine increases, the cystocele recurs, and further operation is carried out There were six such cases in the present series

Mrs A, aged 76 —Complaining of difficulty of micturition for 50 years, since the birth of her first child Had colporrhaphy and amputation of cervix 28 years ago Symptoms of urinary difficulty persisted and another colporrhaphy was carried out in 1957 Afterwards seen by me and found to have residual urine of 30 oz I had no doubt she had been suffering from chronic retention of urine for many years Endoscopy showed marked swelling of the tissue round the bladder neck, which was projecting into the urethra like prostatic lobes The bladder was very trabeculated A transurethral resection of the bladder neck was carried out and 2 g removed Histological report of the excised tissue showed hyperplastic but regular transitional epithelium with fragments of smooth muscle There was considerable infiltration of the submucosa with lymphocytes, eosinophils, and plasma cells Patient had urethral catheter drainage for 5 days Has since passed urine without any difficulty, and now, 18 months later, the residual urine is only 3 oz

I believe such misdiagnosis is common Colporrhaphy can, of course, also cause urethral stricture, of which I have seen several examples, but none are included in this series, which are of bladder-neck obstruction only

Postoperative Retention

As in the male sex, a patient with well-compensated bladder-neck obstruction may develop retention of urine on being confined to bed Thus, in my series, three cases occurred after operation (one herniorrhaphy and two cataract operations) whilst one patient was suffering from a fractured neck of the femur and two from severe rheumatoid arthritis Moore (1952) suggested that postoperative cases should be avoided by more care in preoperative diagnosis, so that the associated bladder-neck obstruction is recognised, and dealt with at the same time as the original lesion

Clinical Features

Essentially these patients complain of difficulty in micturition, which, as in the male, comprises difficulty in starting the act, particularly when the bladder is full, and a lack of force in the flow As residual urine increases in amount, frequency of micturition becomes troublesome. Sometimes secondary infection leads to dysuria, frequency, and, occasionally, hæmaturia Renal obstruction may even be such that uræmia develops

I have divided my cases into the following clinical types

1	Difficulty of micturition	6	(9)
2	Acute retention	4	(8)
3	Chronic retention	7	(7)
4	Chronic retention with incontinence	3	(6)
5	Cystitis	3	(23)
6	Hæmaturia	3	(5)
7	Uræmia	2	(3)
8	Postoperative retention	3	(3)
9	Enuresis	2	(6)
10	Abdominal tumour	0	(15)

This clinical classification is based on the presenting symptom, but most cases also had other symptoms The figures in parentheses relate the total number of patients in the series having each separate symptom

A familiarity with diseases of the urinary tract in the female has protected me from mistaking the chronically distended bladder for an abdominal tumour Trafford (1959) recently described such a case as an example of atony of the bladder Occasionally in both sexes patients with definite urinary obstruction do not appreciate the change in micturition which has taken place, and their presenting symptom may be that of abdominal swelling In the male I have encountered this three or four times, but in this series of females there was no such case.

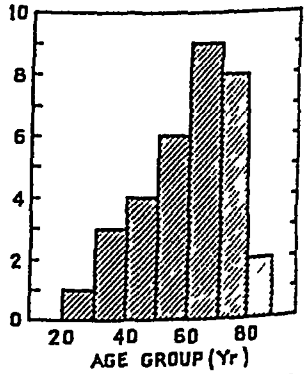

Fig 3—Age incidence of bladder-neck obstruction in the female in 33 cases

The age incidence is interesting (fig 3), varying from 20 to 84 years The condition is most common in the prostatic age-groups, 50, 60, and 70 years Six patients were unmarried

Diagnosis

The diagnosis is missed more often through lack of knowledge of the occurrence of urinary obstruction in the female than through carelessness in clinical examination.

As in the male, most of the symptoms of urological disease can be primarily caused by a bladder-neck obstruction Thus, although chronic retention may be obvious, the distended bladder may be mistaken for an ovarian cyst (Trafford 1959) With awareness of the

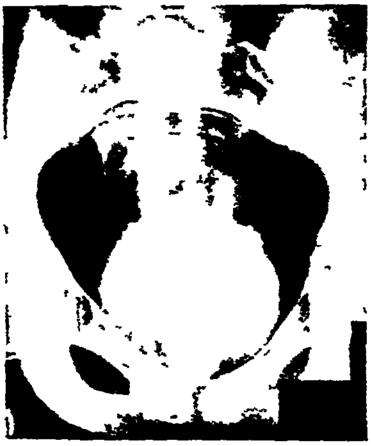

Fig 4—Patient, aged 31, with chronic retention of urine due to bladder-neck obstruction. Intravenous cystogram taken after micturition, showing residual urine.

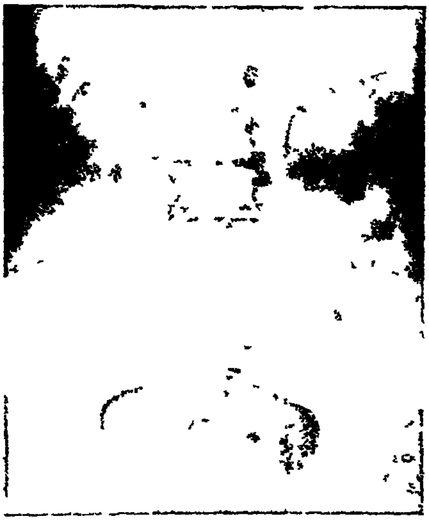

Fig 5—Same patient. Intravenous urogram showing dilatation of both ureters and pelves

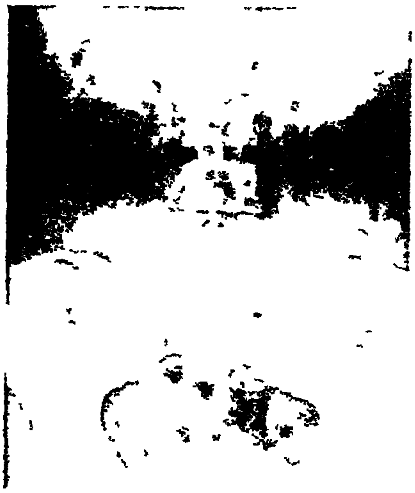

Fig 6—Same patient. Intravenous urogram showing disappearance of ureteric and pelvic dilatation after transurethral resection of bladder neck.

occurrence of urinary obstruction in the female, the diagnosis in such cases (groups 2 and 3) is obvious More often it must be demonstrated by detailed investigation. Estimation of the amount of residual urine—by bimanual examination, urethral catheterisation, and/or intravenous cystography after micturition—is essential (fig 4) Renal dysfunction (fig 5) and urinary infection are demonstrated by the usual methods Cystourethroscopy is the most important procedure. As the instrument is passed along the urethra, a ledge may be felt at the bladder neck. On inspection a prominent lip can be seen in the posterior quadrant—as a median bar, or forming a collar round the bladder neck. Occasionally hypertrophied glandular tissue may bulge into the urethra, like prostatic lobes The mucosa covering the bladder neck in some cases is white and rigid, more often, as is so common in the female urethra, it is swollen, œdematous, and polypoid. These latter changes are not associated per se with obstruction, but are due to concomitant longstanding inflammatory change in the urethra or are caused by inlying urethral catheter

In no case have I been able to appreciate any thickening on palpation of the bladder neck against the pubes or the cystoscope. It is not uncommon, however, to feel thickening in the urethra itself, from associated chronic inflammatory changes or previous operation. On one occasion changes seen suggested carcinoma, and this was subsequently confirmed.

The most important examination is inspection of the bladder neck under local anæsthesia. Normally during attempted micturition one can see that all quadrants of the bladder neck will move proximally and laterally In patients with severe bladder-neck obstruction no movement at all will take place, and with various degrees of obstruction various limitations of the excursion of the bladder neck can be appreciated.

Differential Diagnosis

One must exclude other causes of urinary obstruction—namely, mechanical obstruction of urethra, neurogenic lesions, and hysteria.

Mechanical Obstruction of Urethra

The causes of mechanical obstruction are

1 *From above*
  - Vesical calculi
  - Pedunculated vesical tumours
  - Ureterocele
  - Diverticulum of bladder

2 *In urethra*
  - In lumen
    - Stone
    - Foreign body
    - Valves and diaphragms
    - Ureterocele of ectopic ureteric orifice
  - In wall
    - Stricture (posttraumatic, postinfective and malignant)
    - Diverticulum
    - Abscess of urethral gland
  - Outside wall
    - Fibroids of body of uterus impacted in pouch of Douglas
    - Ovarian cyst impacted in pouch of Douglas
    - Retroverted gravid uterus
    - Carcinoma of cervix
    - Fibroids of cervical canal

All these lesions can be easily identified by careful clinical examination combined with radiological and endoscopic examination where necessary Lesions of the uterus do not cause urethral obstruction directly unless they arise from the cervix, when, as they enlarge, they stretch and compress the urethra. The same effect can be caused by mobile swellings of the uterus itself or of the ovaries when they are sufficiently large and become impacted in the pouch of Douglas Thus, a fibroid of the body of the uterus, or an ovarian cyst which is freely mobile in the abdominal cavity, cannot be the cause of retention of urine.

Neurogenic Lesions

In every case one must suspect a neurogenic cause. Many of my cases, and all in which there has been any doubt, have been seen by a neurologist Usually it is quite clear when any organic nerve lesion is present. Occasionally the presence of a concomitant disease, which could possibly involve the bladder innervation, makes diagnosis extremely difficult, and one may be in doubt whether the obstruction at the bladder neck is primary or secondary to a neurological lesion. When much residual urine is present in a case of neurogenic bladder, transurethral resection of the bladder neck is often the most satisfactory method of therapy When, therefore, such a case is mistaken for primary bladder-neck obstruction no great harm has been done. The result in such cases, however, is not as good as in those with primary bladder-neck obstruction.

In one of my cases of neurogenic bladder the early clinical findings were very difficult to assess and a transurethral resection of the bladder neck was carried out to relieve what was thought to be a case of primary bladder-neck obstruction with a moderate residual urine. The immediate result was very satisfactory, but, during the three years which have since elapsed, it has become apparent that the patient has disseminated sclerosis affecting particularly her lower limbs and bladder. The transurethral resection, however, has done no harm and has ensured that the amount of residual urine present is as small as possible.

In another case the immediate result was very unsatisfactory and a large amount of residual urine remained. As this patient had also Paget's disease of the spine, one wondered whether some secondary effect on the bladder innervation was really the cause of the urinary difficulty. However, after four transurethral resections the patient is now symptom-free and the residual urine has been abolished.

A patient suffering from diabetes with a raised cerebrospinal-fluid protein was completely cured after a transurethral resection of the bladder neck.

Hysteria

Hysteria is the hardest condition to exclude. I do not deny that sometimes it is the cause of urinary difficulty, but I believe that many of these patients are really suffering from bladder-neck obstruction. This is confirmed by the trabeculated bladder and the definite obstructive changes at the bladder neck. When such changes are present transurethral resection can be recommended with confidence.

Miss B, a nurse aged 20, complained of enuresis. She had been seen by many psychiatrists. Investigations showed a much trabeculated bladder with a primary bladder-neck obstruction. The residual urine, estimated on several occasions, was 10 oz. Transurethral resection of the bladder neck was carried out with excellent result. No residual urine and no further enuresis.

Another condition which I have not mentioned and of which I have had no experience is primary atony of the bladder. Trafford (1959) reported four cases. It is very difficult to be sure of this condition. It is not unlikely that in the reported cases minor changes at the bladder neck causing chronic retention have been missed. To the uninitiated the obstructive lesion is very hard to diagnose, and very little change at the bladder neck can cause severe obstruction. It is really astonishing sometimes how little has to be done to the bladder neck to put things right. Occasionally, when the residual urine has remained high after transurethral resection, I have wondered whether the primary lesion has not been atony of the bladder. Biopsy, however, has never confirmed that there was anything wrong with the bladder muscle per se. These cases are really examples of secondary atony of the bladder following long-continued distension.

Unrelated Diseases Present

Concomitant diseases have been

Holmes-Adie syndrome	1	Hysteria	1
Solitary cyst of kidney	1	Fractured neck of femur	1
Rheumatoid arthritis	2	Papilloma of bladder	1
Paget's disease of spine	2	Uterine fibroid	1
Colporrhaphy	6	Abdominoperineal excision	1
Hypertension	2	Diabetes	1

There are two ways in which these are important. Firstly, as already mentioned, some may possibly be responsible for neurogenic lesions, which may account for the bladder symptoms. In none of the cases in this series, however, was there any such effect. Secondly, others may precipitate the onset of retention of urine. This happened after an abdominoperineal excision of the rectum in one patient and required treatment, just as in the male the prostate often requires treatment in such circumstances. In other patients injury, disease, or operation led to confinement to bed with exacerbation of previously slight symptoms of primary bladder-neck obstruction.

Treatment

Of the thirty-three cases four were treated conservatively and twenty-nine by transurethral resection of the bladder neck.

When obstruction causes severe renal dysfunction, preoperative treatment by indwelling urethral catheter may be necessary. In severe secondary infections a few days' administration of the appropriate antibiotic or sulphonamide, with catheter drainage, will make operation safer. Not all cases require operation. Thus four patients who had very definite obstruction (proved by complete investigation) recovered urinary function after a short period on catheter drainage; the residual urine was not large and operation was not carried out. These patients have been under observation for several years and so far none has required any further treatment, though they may do so some day. Such a state of affairs is exactly comparable to that in the male where the bladder-neck lesion often responds to conservative measures, and no further action is necessary beyond careful observation. Where there is definite residual urine, however, and of course where retention is present, treatment must obviously be undertaken.

In resecting the bladder neck I use a Thompson punch. This is an excellent instrument but must be used with even greater care in the female than in the male, because the distance between the urethra and the vagina is so small. I take great care to remove bites no more than 1 cm long, and with a finger in the vagina I can judge the depth of cut in the posterior quadrant. Where changes are right round the bladder neck, resections are made circumferentially. The amount has varied between 1 and 2 g. It is astonishing in some cases, however, how little has to be done. In the great majority one resection has put the patient right, one patient required two, another three, and another four resections.

Postoperative Complications

A vesicovaginal fistula may be formed by cutting too deeply, or later by using too much diathermy in securing hæmostasis. Incontinence of urine is due to cutting too distally in the urethra, and likewise can be avoided by care. The only other complications are associated with urinary infection, which is usually present before operation. A satisfactory resection and the appropriate antibiotic are the best means of overcoming it.

Results

In thirty of the thirty-three cases the results were good. Of the four cases treated conservatively, all are doing well so far. Of the twenty-nine treated by transurethral resection, twenty-six have been relieved of the symptoms of urinary obstruction, while residual urine has been reduced or abolished and urinary infection has been overcome (fig 6). For a few days after the catheter is taken out, many patients have slight incontinence, but this soon disappears. After the resection the bladder is usually drained with an indwelling urethral catheter for 5 days. When, however, the patient has had a large residual urine for many years it is of course impossible for the bladder to recover tone in this short time. In long-standing cases, therefore, the catheter has often had to be replaced and left for varying periods, and afterwards the residual urine has often had to be checked daily until the bladder muscle eventually recovered. Occasionally in the male sex where there is gross secondary atony with a very large residual urine which does not diminish after long-continued drainage it may be necessary to carry out a partial cystectomy to reduce bladder capacity and increase intravesical pressure and sensitivity. I have not yet seen such a case in a woman, but such therapy might occasionally be required.

One patient suffering from a carcinoma of the bladder neck had to be treated surgically.

In two cases results have been poor. One was an old lady of 78 in whom I caused a vesicovaginal fistula; this was repaired by operation. She made satisfactory progress but died eventually from ascending urinary infection. The second case illustrates the difficulties that may be encountered.

Mrs C, aged 62. Previous history of failed colporrhaphy for stress incontinence. Admitted to hospital in uræmia—very thin and emaciated. Blood-urea 83 mg per 100 ml. Intravenous urography showed considerable dilatation of both pelves and ureters. Urine contained numerous white blood-cells with a moderate growth of *Escherichia coli* on culture. With catheter drainage, condition improved remarkably. Investigations showed large residual urine and obstruction at the bladder neck. Transurethral resection relieved obstruction and abolished residual urine. Normal control of micturition except she still had stress incontinence. Gynæcological opinion sought and further colporrhaphy performed. After this she developed total incontinence of urine!

Some time later, in an attempt to cure the incontinence, I carried out a urethral-sling operation without success. Eventually, because she was in such a miserable state, an ileal conduit had to be made. With this, her general condition improved and the conduit was satisfactory. She still, however, was a very poor soul and complained of vaginal discharge. After long-continued gynæcological treatment, this did not clear up, and eventually it was found that the discharge was really coming from her infected bladder. As this did not clear up after prolonged continuous irrigation through a two-way indwelling catheter, the bladder finally had to be removed. It was just an abscess cavity. After this the patient's condition improved and she was discharged home.

Later she had the misfortune to fall and break her femur. After many months in hospital she was discharged home in fair condition, only to contract bronchopneumonia, from which she died.

Summary

Bladder-neck obstruction in the female is a very real condition, just as definite as prostatic obstruction in the male. It can cause many types of urinary symptoms and may lead to severe renal dysfunction. A well-performed transurethral resection not only relieves symptoms but restores the urinary tract to a healthy state.

I should like to record my indebtedness to Dr G. W. Ollerenshaw and the members of the department of medical illustration at the Manchester Royal Infirmary for their help in the preparation of the illustrations, also to Dr J. W. Huffman and the American Medical Association for allowing me to reproduce fig. 2.

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ANTICOAGULANT DRUGS IN THE TREATMENT OF PULMONARY EMBOLISM

A CONTROLLED TRIAL

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THE use of an anticoagulant drug in treating venous thrombosis was first reported by Murray et al. (1937) and Crafoord (1937), who administered heparin, and soon there were claims that the number of deaths from pulmonary embolism was thereby reduced.

Bauer (1946) cited 71 cases of pulmonary embolism treated with intravenous heparin with no deaths. Because of the high cost of heparin and the disadvantage of repeated intravenous injections, longer-acting anticoagulant drugs of the coumarin type came into more widespread use. Allen et al. (1947) reported 329 cases of pulmonary embolism treated with heparin and dicoumarol with only 1 death. Bauer (1959) has reported 627 cases of venous thrombosis, treated with heparin alone, with only 5 deaths from pulmonary embolism. Of the 45 other patients who had already had one pulmonary embolism 2 died.

In a retrospective survey covering thirteen years, Barker et al. (1940) found evidence of venous thrombosis or pulmonary embolism in 0·96% of 172,888 postoperative cases untreated with anticoagulants; more than half of their patients with pulmonary embolism died. In other series the mortality in cases of pulmonary embolism has been high. de Takats and Jesser (1940) and Short (1952) reported a mortality of 87% and 23% respectively.

The diagnosis of pulmonary embolism is rarely proved before death. The diagnosis in life rests on a combination of symptoms and signs in the chest and legs and changes in the radiogram and electrocardiogram, and in the less severe cases the diagnosis is more uncertain. For this reason it is unsatisfactory to compare results in series reported by different workers.

There are other objections to this type of comparison. Sudden death is common in pulmonary embolism, and untreated series include patients who died before any effective treatment could have been given. In other cases the diagnosis, unsuspected in life, is made only at necropsy. Cases of these two types will not figure in any treated series.

The risk of hæmorrhage has made many physicians and surgeons unwilling to use anticoagulants routinely in the treatment of pulmonary embolism on existing evidence. There is some further support for scepticism of the protection afforded by anticoagulants in a report by Marks et al. (1954). They reported favourably on the value of anticoagulants in cases of venous thrombosis but found that it did not reduce the incidence of fatal pulmonary emboli. Once pulmonary embolism has occurred it may appear to be too late for anticoagulants to be effective.

Our object has been to measure the effect of anticoagulants in patients who have had one pulmonary embolism, both on the course of the first embolism and on the risk of further attacks. It seemed essential to use the method of observing concurrent series of patients, deciding by chance whether they received anticoagulants or not.

Material and Methods

Selection of Patients

Medical and surgical colleagues were asked to notify us at the first indication that pulmonary embolism might have occurred in any of their patients. Full clinical examination carried out without delay and a portable chest radiograph and electrocardiogram were taken The clinical features on which the diagnosis was based reflected the presence of acute right-sided heart-failure or of pulmonary infarction or both Right-sided heart-failure usually declared itself with faintness, central chest pain, a fall in blood-pressure, and a rise in jugular venous pressure together with changes in the electrocardiogram When pulmonary infarction occurred the common findings were pleuritic pain, hæmoptysis, fever, pleural friction, loss of resonance at the lung base, and rales, in these patients it was usual to find changes in the bedside chest radiograph Tenderness or swelling of the calf or any other signs of thrombophlebitis strengthened the diagnosis, but some of the patients had no abnormal signs in the legs The clinical features, electrocardiograms, and radiographs of these patients will be fully described in a separate report

When pulmonary embolism was diagnosed, the suitability of the patient for anticoagulant treatment was considered The only contraindications to anticoagulants were (*a*) a recent operation, and (*b*) a history suggestive of recent peptic ulceration If pulmonary embolism had occurred within a week of an operation the surgeon in charge of the case was asked if anticoagulants could be used Anticoagulants were seldom withheld except after such operations as mastectomy or prostatectomy where a large raw area had been left If it was considered that the risk of hæmorrhage was too great the patient was excluded from the series The fact that a patient was thought to have had more than one episode of pulmonary embolism did not exclude him The time that elapsed between the first symptom and inclusion in the trial varied from a few minutes to as long as twelve days It was within twenty-four hours in 41 out of 73 cases

Envelopes were prepared containing an equal number of cards marked " anticoagulant " or " no anticoagulant ", and when a patient was admitted to the trial a card was drawn

Treatment

All patients were confined to bed for ten days There were a few whose condition did not allow them to begin to walk on the tenth day The remainder were encouraged to walk increasing distances and then return to bed, sitting in a chair was forbidden Where there were signs of venous thrombosis in the leg the foot of the bed was elevated and a cradle used to prevent pressure from bedclothes Some patients in both groups were given oxygen therapy for severe breathlessness or cyanosis, pressor drugs (L-noradrenaline and mephentermine sulphate) for severe hypotension, and digitalis for atrial fibrillation or paroxysmal tachycardia Antibiotics were not usually given for pulmonary infarction

TABLE I—ANTICOAGULANT DOSAGE SCHEME

Actual prothrombin-time (sec.) / Control prothrombin-time (sec)	Dosage for next 24 hr *
4–6	½ of total dose previous day
4–3	¾ ,, ,, ,, ,, ,,
3–2	Whole ,, ,, ,, ,, ,,
2–1½	1¼ times ,, ,, ,, ,,
Under 1½	1½ times ,, ,, ,, ,,

* Divided into two roughly equal doses, given night and morning

Those who were to have anticoagulants were treated with heparin and nicoumalone (' Sinthrome ') Heparin was given by intravenous injection 10,000 units every six hours for six doses, without laboratory control Nicoumalone was begun concurrently and the prothrombin-time estimated by the one-stage Quick test on the third day Nicoumalone was usually given in the following doses 16 mg followed at twelve-hourly intervals by 8, 8, and 4 mg The dose was then regulated to maintain the prothrombin-time at between two and three times control time Table I shows the dosage used

It was never necessary to give an injection of protamine sulphate to counteract the effect of heparin Vitamin K_1 was administered—probably unnecessarily—to 3 patients who had minor hæmorrhages Anticoagulants were given for fourteen days except to those who bled and 1 other patient who was thought to have developed drug sensitivity 5 patients received a longer course of anticoagulants for periods up to twenty-eight days because they were unable to get up from bed on the tenth day

Findings

The first patient was admitted to the trial in March, 1957 By April, 1958, 35 patients had been included, and at this stage it became necessary to review the further conduct of the trial Of 19 patients who had not received anticoagulants 5 had died of pulmonary embolism Of 16 who had received anticoagulants none had died of pulmonary embolism, and 1 had died of suppurative pneumonia with hæmorrhage from a duodenal ulcer as a contributory factor In addition 5 others in the untreated group had non-fatal recurrences of pulmonary embolism. In the treated group there was no recurrence

TABLE II—RESULTS IN FIRST 35 CASES

Group	Total	Deaths from pulmonary embolism	Non-fatal recurrences	Other deaths
Untreated	19	5	5	0
Treated	16	0	0	1

First Stage of Trial (35 cases)

An analysis of the results (table II) showed that the difference in deaths in the two groups from pulmonary embolism was unlikely to be due to chance P=0 036 (1 in 28) When deaths from pulmonary embolism and non-fatal recurrences were taken together the result was convincing P=0 0005 (1 in 1987)

In view of this situation it was felt that the trial could not be continued in its original form The low mortality in the treated series, however, needed confirmation Accordingly the trial was continued with the same criteria for inclusion, but thereafter all patients were to receive anticoagulant treatment By July, 1959, a total of 54 patients had been treated with anticoagulants and the trial was stopped

Complete Series (73 cases)

To test the significance of the results (table III) the following comparisons were made

Deaths from pulmonary embolism —Untreated cases 5 out of 19, treated cases 0 out of 54 P=0 0007 or 1 in 1292

Deaths from pulmonary embolism added to non-fatal recurrences —Untreated cases 10 out of 19, treated cases 1 out of 54 P=0 0000014 or 1 in 704,225

Deaths from all causes —Untreated group 5 out of 19, treated group 2 out of 54 P=0 011 or 1 in 90

Deaths

The 5 deaths in the untreated group were all due to pulmonary embolism

Case 1 —A woman of 56 with carcinoma of the breast and pelvic metastases Massive pulmonary embolism occurred four days after admission to hospital and was followed by steadily increasing signs of infarction of both lungs The patient became increasingly dyspnœic and produced terminally large quantities of very offensive sputum She died twenty-one days after the first symptom of embolism, and necropsy showed massive pulmonary infarction with cavitation There were large, organising clots in both main pulmonary arteries but no very recent thrombi

TABLE III—RESULTS IN COMPLETE SERIES OF 73 CASES

Group	Total	Deaths from pulmonary embolism	Non fatal recurrences	Other deaths
Untreated	19	5	5	0
Treated	54	0	1	2

Case 2.—A man of 56 who five days after a second laparotomy for intestinal obstruction developed very severe constricting central chest pain and signs of right-sided heart-failure The presence of extensive thrombophlebitis of the leg and the recurrence of slight hæmoptysis pointed to the diagnosis He survived for forty-eight hours after massive pulmonary embolism In addition to the thrombophlebitis of the leg, large clots were found in the hepatic veins that were thought to be the result of pylephlebitis

Case 3.—A 78-year-old woman had severe pulmonary embolism twenty-one days after an operation to reduce a Pott's fracture. She died suddenly twelve days later, and necropsy revealed large fresh clots in the main pulmonary artery

Case 4.—A man of 57 who had had a cerebral thrombosis six years previously developed thrombophlebitis of the right leg Right pleural pain and hæmoptysis led to the diagnosis of pulmonary embolism, and he was admitted to the trial One day later sudden breathlessness, severe hypotension, and obvious electrocardiographic changes gave evidence of a second large embolism He developed increasing signs of bilateral pulmonary infarction with fœtid sputum and swinging fever He survived for fifteen days after the second episode At necropsy there were large clots in both pulmonary arteries and massive infarction of the lower lobes of both lungs with cavitation

Case 5.—A 41-year-old man survived for fourteen days after the first symptoms of pulmonary embolism He had been admitted to hospital for treatment of the nephrotic syndrome Six days before his death signs of acute pulmonary œdema developed, but he recovered from this attack and improved after treatment with diuretics He died during a major epileptic fit. Necropsy showed that his renal disease was due to primary amyloidosis Large clots were found in the pulmonary arteries, and in the left lower lobe the pulmonary vein was filled with clot which was continuous with a mass of clot 6 cm × $3^{1}/_{2}$ cm × $3^{1}/_{2}$ cm lying in the left atrium. Emboli were found saddling the bifurcation of both common carotid arteries Pulmonary œdema had presumably been caused by the obstruction in the left atrium, and the immediate cause of death was cerebral infarction

Of the 2 deaths in the treated series which are now to be described, the 1st was due to suppurative pneumonia complicated by hæmorrhage from a duodenal ulcer, and the 2nd was due to anuria resulting from necrosis of the renal tubules of unknown cause

Case 6.—A woman of 68 years, known to have hypertension, was admitted to a mental hospital with a diagnosis of depression Intestinal obstruction was found, and she was transferred to this hospital where a strangulated hernia was repaired. After operation she ran a very low-grade fever and on one occasion auricular fibrillation was thought to have developed An electrocardiogram on the same day showed sinus rhythm Six days after operation she complained of severe right pleural pain of sudden onset Friction was to be heard, and there were dullness to percussion, and rales at the right base She coughed blood-stained sputum which increased in amount A portable chest X-ray showed extensive shadowing at the right base and mid-zone. Electrocardiography revealed hypertensive changes only

No adequate history could be obtained from the patient She was admitted to the trial, and after a card had been drawn anticoagulants were begun Supervision of the dosage of nicoumalone was inadequate, and on the fourth day of treatment her prothrombin-time was prolonged to eight times normal Again on the sixth day it was between five and six times normal

Her condition deteriorated and greater quantities of purulent sputum were produced On the ninth day of treatment melæna was noticed and anticoagulants were stopped She died on the following day Necropsy revealed suppurative pneumonia with abscess formation which was presumed to have followed inhalation of vomit. There was also a subacute duodenal ulcer in the base of which a small artery had been eroded. Considerable intestinal hæmorrhage had occurred Minor pulmonary emboli were found, and there were ante-mortem thrombi in the calves of both legs and in the right long saphenous vein Suppurative pneumonia was considered to be the major cause of death, but intestinal bleeding was an important contributory factor, and this death has therefore been classified as due to treatment

Case 7.—A man of 52 developed superficial thrombophlebitis of the left leg for which he was given phenylbutazone This was discontinued when an erythematous rash developed Three weeks later superficial thrombophlebitis appeared in the right leg, followed in a further two weeks by pulmonary embolism He was later admitted to hospital where superficial thrombophlebitis of the left long saphenous vein, tenderness of both calves, and bilateral pulmonary infarction were found During eighteen days' treatment with phenindione the signs of pulmonary infarction and of phlebitis subsided and he was discharged home. Two weeks later he was readmitted with pleural pain and was found to have pain and swelling again in both calves and signs of bilateral pulmonary infarction There was no fall in blood-pressure He was admitted to the trial and treatment was begun with heparin and phenindione. That phenindione rather than nicoumalone had mistakenly been prescribed was not realised for several days, and it was then thought that the treatment should continue unchanged In addition to phenindione, butobarbitone was also given at night. On the twelfth day of treatment a generalised erythematous rash appeared, followed by fever and diarrhœa. All drugs were withheld. Oliguria and later anuria developed, and the blood-urea rose to 560 mg per 100 ml He died suddenly four weeks after the appearance of the skin rash which followed the second course of phenindione Necropsy confirmed the diagnosis of thrombophlebitis of both legs and old pulmonary infarction Death was due to extensive renal tubular necrosis and uræmia

The cause of the renal lesion is unknown There was no period of hypotension It was felt that the skin eruption could have been due to sensitivity to the phenindione or butobarbitone which he was taking

Recurrences

In the first stage of the trial there were during the trial period (i e, fourteen days) 5 non-fatal recurrences of embolism in the untreated group and no recurrences in the treated group Among the 54 treated patients in the complete series there was 1 non-fatal recurrence

Subsequent Progress

After the trial period it was not possible to keep all the patients under review The fate of the 29 survivors of the first period of the trial is known In 1 of the untreated group a further embolism developed eight weeks after the trial period, following a second operation on her fractured neck of femur This was the only recurrence in a follow-up ranging from twelve to twenty-four months 2 of the patients in the later series were readmitted to hospital with recurrence of infarction in the fourth week after completing the fourteen-day course of anticoagulant treatment

Effect of Anticoagulants on Leg Vein Thrombosis

No attempt was made to assess the progress of the venous lesions of the legs in all patients with tenderness or swelling In 3 patients who were being treated with anticoagulants there was obvious extension of superficial thrombophlebitis

Severity of Cases in the Two Groups

Evidence of stress on the right side of the heart indicates that the embolism is massive (Wood 1950) In all the cases records were kept of the presence or absence of a significant fall of blood-pressure and of severe electrocardiographic changes, and these were the two criteria we have used in defining which cases were " severe " and which were not The changes which were sought in the electrocardiogram were those described by Cutforth and Oram (1958), inversion of the T waves in leads II, AVF and V_2, and the presence of right bundle-branch block Using these criteria there were 20 severe cases All had a considerable fall in blood-pressure, 15 fulfilled both criteria, and in 1 other the electrocardiographic evidence of severity was dubious The distribution of the severe cases was similar in the two groups

Severe cases—Untreated cases 6 out of 19, treated cases 14 out of 54 χ^2 (with Yates' correction)$=0{\cdot}031$ $0{\cdot}8<P<0{\cdot}9$

Lung Changes with Stress on Right Side of Heart

Of the 20 patients with evidence of stress on the right side of the heart, some later had massive pulmonary infarction while others showed neither clinical nor X-ray evidence of this Lung changes were more in evidence in the 6 severe cases from the untreated group Of these 6, 2 died (cases 1 and 4) of massive pulmonary infarction with virtual dissolution of the lower zones of both lungs Nothing like this was seen in any of the treated cases Of the remaining 4 severe cases in the untreated group, 1 died within forty-eight hours and 2 of the other 3 had extensive pulmonary infarction but recovered Of the 14 severe cases in the treated group, 2 recovered without clinical signs or X-ray evidence of infarction and in 2 others only a few rales and no radiographic changes developed Thus anticoagulants appeared to diminish the extent of pulmonary infarction.

Mistaken Diagnoses

The diagnosis was proved wrong in case 6 (already described) and in 1 other patient who came to necropsy Again suppurative pneumonia following œsophageal rupture after instrumentation was found No anticoagulants had been given, and this patient does not therefore figure in the final analysis of the results

Discussion

The first conclusion drawn from this trial is that in a patient who has already had pulmonary embolism the subsequent course of the disease is affected by the regime of anticoagulant therapy we have used the mortality of pulmonary embolism is reduced The results show that deaths from pulmonary embolism are likely to outnumber the deaths that may be attributed to treatment

In the *treated group* we have assumed that the 1 fatal case of renal tubular necrosis was caused by the anticoagulant drug In the other fatal treated case other factors were important in causing death

Of the 5 deaths in the *untreated group* only 1 followed immediately the lodging of a second embolism in the pulmonary artery (case 3) In 1 other a second embolism occurred the day after his inclusion in the trial, but the patient lived a further fifteen days (case 4) In the others, only one episode of embolism was diagnosed and the three patients lived for two, fourteen, and twenty-one days 2 of the 5 deaths were due to very extensive pulmonary infarction with superadded infection and cavitation In another, death was due to extension of the thrombus through the pulmonary veins to fill the left atrium These 5 cases suggest that the idea that it is too late to use anticoagulant treatment when a pulmonary embolism has already occurred is ill founded

There were no comparable deaths in the treated group, even in the most severe cases, and it seems reasonable therefore to conclude that even after embolism has reached the pulmonary arteries anticoagulant therapy reduces the risk of death from heart-failure or from pulmonary infarction—probably by discouraging further deposition of thrombus in the pulmonary arteries where the blood-flow is so grossly impeded This would explain its effect in diminishing the extent of subsequent pulmonary infarction

2 patients died very quickly after the first signs of embolism We have, however, been impressed by the fact that every patient in this series who received the first injection of heparin survived This suggests that there is no longer any place for considering Trendelenburg's operation of pulmonary embolectomy One of our patients required long-continued infusions of L-noradrenaline, and several others required repeated intravenous injections of mephentermine sulphate to maintain the blood-pressure. All subsequently recovered No instance of chronic cor pulmonale has yet been diagnosed in these cases

The diagnosis of pulmonary embolism can never be established with absolute certainty during life, and there is always a risk of mistakenly treating postoperative pneumonia with anticoagulants This not only entails additional risk, but also deprives the patient of the benefit of specific treatment Case 6 shows that the two conditions may arise in one patient at the same time

Without close supervision of the administration of the anticoagulant, unnecessary deaths may occur, as in case 6, who had extensive intestinal hæmorrhage at a time when the prothrombin-time was unduly prolonged

Summary

73 patients in whom pulmonary embolism had been diagnosed and in whom there was no contraindication to anticoagulant therapy were admitted to a clinical trial One group were to receive treatment without anticoagulants, and the other heparin and nicoumalone ('Sinthrome') The treatment period was fourteen days

In the first 35 patients a card was drawn to decide whether anticoagulants should be used or not Of the 19 untreated cases 5 died and 5 others had non-fatal recurrences of embolism Of the 16 cases treated with anticoagulants 1 died and none had recurrences of embolism. The 1 death in the treated series was due to a combination of suppurative pneumonia and alimentary bleeding

No further cases were admitted to the untreated series, but 38 others were taken into the treated group, making a total of 54 There was only 1 further death, and this was due to renal tubular necrosis in a patient mistakenly treated with phenindione instead of nicoumalone

It is concluded that when a patient has had pulmonary embolism, heparin and nicoumalone reduce the risk of death from that embolism The likelihood of recurrent embolism is also diminished

Prof C Bruce Perry, Dr J E Cates, Dr D H Davies, Dr J E G Pearson, and Dr J A Cosh suggested the form of this trial and the type of treatment that should be tested We are indebted to them, and to all the physicians and surgeons of the United Bristol Hospitals who allowed us to include their patients

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Addendum

Since this paper was completed R H Brooks and H B Calleja (*Ann intern Med* 1960, 52, 706) have reported the occurrence of a nephropathy accompanying a generalised sensitivity reaction to phenylindione Their patient developed fever, hepatitis, and a rash; and the urine contained albumin, casts, and red blood-cells Recovery was complete

A PITUITARY-DEPENDENT INHIBITOR OF GLUCOSE UPTAKE BY MUSCLE IN PROTEIN FRACTIONS OF HUMAN PLASMA

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WHEN protein fractions are prepared from normal human serum by zone electrophoresis on columns of treated cellulose, insulin may be detected in fractions containing α_1-globulins, β-globulins, and γ-globulins by their stimulating effect on the uptake of glucose by isolated rat diaphragm (Randle and Taylor 1958, Taylor and Randle 1959) During these experiments we noted that whereas some α_2-globulin fractions stimulate uptake of glucose, others depress it or are without effect. Since the α_2-globulins migrate on electrophoresis between fractions containing substantial amounts of insulin (albumin+α_1-globulin and β-globulin fractions), it seemed possible for an inhibitor of glucose uptake to be present in α_2-globulin fractions, but for its activity to be masked in some samples by insulin derived from adjacent fractions This expectation has now been realised in experiments in which α_2-globulins were more effectively separated from normal human plasma by a combination of fractional precipitation with ethanol and zone electrophoresis Since α_2-globulins prepared from plasma in this way have consistently inhibited the uptake of glucose by diaphragm, it seemed important to test similar protein fractions prepared from the plasma of hypophysectomised patients and from patients with panhypopituitarism both before and after treatment with human growth hormone (H.G H) We here present the results of these experiments

Methods and Procedure

Blood Samples

Blood was collected from an antecubital vein with a clean dry syringe and diluted immediately with acid-citrate-dextrose (A.C.D) 0 173 volumes (Lever et al. 1951) The A.C.D -plasma was then separated by centrifugation.

Patients

Blood samples were collected from hypophysectomised patients or from patients with panhypopituitarism who were maintained on cortisone and thyroxine. Blood samples from diabetic hypophysectomised patients were collected about 24 hours after the last injection of insulin zinc suspension ('Lente') When H G H was given (5 or 10 mg by subcutaneous injection) blood was collected 18–24 hours after injection of the hormone. The H.G H used in these studies was prepared from human pituitaries by methods already described (Taylor and Randle 1959)

Preparation of Protein Fractions

The proteins of A.C.D -plasma were separated into three fractions by fractional precipitation with cold ethanol after the method of Lever et al (1951) The fractions were dialysed at room temperature against distilled water, and then freeze-dried. They are designated according to Lever et al. at I–III (mainly α_2 and β globulins and fibrinogen), II (γ-globulins), and IV, V, and VI (mainly albumin and α-globulins, with some β-globulins) The composition of these fractions was confirmed by paper electrophoresis using the technique of Flynn and de Mayo (1951) and the protein-staining method of Henry et al. (1957)

Subfractionation of IV, V, and VI—Fraction IV, V, and VI, prepared as above, was subfractionated by zone electrophoresis on columns of treated cellulose, using an improved method (Naughton and Taylor 1960) Three subfractions were separated (albumin+α_1-globulins, α_2-globulins, and β-globulins), dialysed at room temperature against distilled water, and freeze-dried

Assay of Biological Activity

The effect of each protein fraction or subfraction on the uptake of glucose by isolated rat diaphragm was tested as described previously (Randle and Taylor 1958) Insulin was deemed to be present if a fraction or subfraction enhanced glucose uptake significantly (Taylor and Randle 1959), and an inhibitor was deemed to be present if glucose uptake was diminished significantly Each fraction or subfraction was dissolved in bicarbonate-buffered salt-solution (Gey and Gey 1936) of three times the volume of the plasma from which the fraction was prepared (for assay of biological activity) Fraction I–III (containing fibrinogen) clotted at this stage, the clot was allowed to form and was then removed by centrifugation.

Results

The effects of protein fractions of normal human plasma on the uptake of glucose by diaphragm are shown in tables I and II Fraction II (γ-globulins) had no demonstrable effect on glucose uptake Fraction I+III (mainly α_2 and β globulins) consistently stimulated glucose uptake The effect of fraction IV, V, and VI (mainly albumin and α_2-globulins, with some β-globulins) was not consistent, whereas many samples inhibited the uptake of glucose significantly, others had no significant effect. When fraction IV, V, and VI was subfractionated by zone electrophoresis, however, the albumin/α_1-globulin subfraction enhanced glucose uptake, whereas the α_2 and β globulin subfractions inhibited glucose uptake Moreover, the sum of the effects of individual subfractions was very similar to that of the fraction from which they were prepared.

TABLE I—EFFECT OF PROTEIN FRACTIONS OF NORMAL HUMAN PLASMA ON UPTAKE OF GLUCOSE BY DIAPHRAGM

Glucose uptake (difference from control incubated in buffer alone) mean difference ± S.E. of difference (mg glucose per g wet diaphragm per hr)

Fraction I–III	Fraction II	Fraction IV, V and VI
1·3±0·25§	0·3±0·3‡	−0·6±0·25*

For differences marked ‡P<0·001, §P<0·01>0·001, *P<0·05>0·01, and for other differences P>0·05

Each difference is derived from means of 36 observations (fractions I–III and II) or 54 observations (fractions IV, V and VI) 6 plasma samples were tested from fractions I–III and II, and 9 plasma samples from fractions IV, V and VI

The effects of protein fractions from the plasma of hypophysectomised patients were noticeably different from those of comparable fractions of normal human plasma. Thus glucose uptake was increased by fraction IV, V, and VI, and by the α_2 and β globulin subfractions thereof, whereas comparable fractions from normal human plasma inhibited glucose uptake. The differences were less with protein fractions of plasma from patients with panhypopituitarism, and some inhibition was seen with the β-globulin subfraction of fraction IV, V, and VI (table II) The effect of hypophysectomy on the inhibitory activity of α_2-globulin and β-globulin subfractions is shown by the results of experiments with plasma from an acromegalic patient before and after hypophysectomy (table III)

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TABLE II—EFFECT ON GLUCOSE UPTAKE OF DIAPHRAGM OF PROTEIN FRACTIONS FROM NORMAL PLASMA AND PLASMA FROM HYPOPHYSECTOMISED PATIENTS, OR PATIENTS WITH PANHYPOPITUITARISM

Source of serum and protein fractions	Case no	Glucose uptake (difference from control incubated in buffer alone) mean difference±S.E. of difference (mg. glucose per g. wet diaphragm per hr.)			
		Fraction IV, V, and VI	Subfractions of IV, V, and VI		
			Albumin+α_1-globulin	α_2-globulin	β globulin
Normal plasma	1–9 (pooled results)	−0·6±0·25			
	7	−0·5±0·29	0·1±0·62	−0·6±0·70	0·1±0·62
	8	−0·4±0·75	1·9±0·48§	−1·5±0·39§	−1·2±0·35
	9	−0·3±0·31	1·5±0·32‡	−0·6±0·39	−1·1±0·34§
	Pooled		1·2±0·29‡	−0·9±0·28§	−0·8±0·25§
Hypophysectomised patients	1	0·6±0·39			
	2	0·1±0·36			
	3	0·7±0·50			
	4		1·8±0·47§	0·4±0·34	1·9±0·36‡
	5		2·2±0·42‡	1·9±0·49§	0·6±0·25‖
	Pooled	0·5±0·28	2·0±0·3‡	1·2±0·28§	1·3±0·21‡
Panhypopituitarism	1	0·0±0·60	1·1±0·67	−0·1±0·49	−0·8±0·56
	2	0·2±0·84	0·4±0·37	0·1±0·32	−0·2±0·37
	Pooled	0·1±0·5	0·8±0·37	0·0±0·27	−0·5±0·31

For differences marked ‡ P<0·001, § P<0·01>0·05, ‖ P<0·05>0·01, and for other differences P>0·05.
Each difference is derived from means of 6 observations. Hypophysectomised patients 2, 3, and 5 were also diabetic.

The effects of H.G.H. on the biological activity of protein fractions of plasma from patients with panhypopituitarism are shown in table IV. Before treatment with H.G.H. none of the protein fractions showed significant inhibitory activity; after treatment significant inhibition was noted with both α_2 and β globulin subfractions. This effect of H.G.H. was greatest with α_2-globulin subfractions.

Discussion

We conclude from the results of our investigations that insulin is present in the albumin/α_1-globulin and β-globulin fractions of normal human plasma, and that an inhibitor of glucose uptake is present in the α_2 and β globulin fractions. The presence of this inhibitor in protein fractions of human plasma seems to depend upon whether pituitary growth hormone is available. Neither insulin nor inhibitor could be detected in γ-globulins.

When zone electrophoresis was previously used alone, insulin was detected in the albumin/α_1-globulin, β-globulin, and γ-globulin fractions, and an inhibitor was occasionally found in the α_2-globulin fractions (Randle and Taylor 1958). In these studies insulin in the γ-globulins may have resulted from contamination with β-globulins containing the hormone, and failure to obtain consistent inhibition with α_2-globulins may have been due to contamination of α_2-globulins with insulin from adjacent fractions. These views were justified by the present investigation, where a more refined method of plasma-protein fractionation yielded γ-globulin fractions which seem to be free of insulin, and α_2-globulin fractions which consistently inhibit the uptake of glucose by diaphragm.

The inhibitor identified in these studies is interesting in relation to growth hormone and its diabetogenic effect in man.

TABLE III—EFFECT OF HYPOPHYSECTOMY ON BIOLOGICAL ACTIVITY OF PROTEIN FRACTIONS OF HUMAN PLASMA

Subfraction of IV, V, and VI	Glucose uptake (difference from control incubated in buffer alone) mean difference±S.E. of difference (mg. glucose per g. wet diaphragm per hr.)		
	Before hypophysectomy	After hypophysectomy	Difference
Albumin + α_1-globulin	0·0±0·42	1·8±0·47§	1·8±0·63
α_2-globulin	−0·8±0·42	0·4±0·34	1·2±0·52
β-globulin	−0·4±0·45	1·9±0·36‡	2·3±0·58§

For differences marked ‡ P<0·001, § P<0·05>0·001, and for other differences P>0·05.
Plasma samples were taken before and after hypophysectomy from an acromegalic patient. Each difference is derived from means of 6 observations.

Experiments have shown that, when rats are treated with ox growth hormone, the in-vitro uptake of glucose by isolated diaphragm and the sensitivity to insulin are reduced (Manchester, Randle, and Young 1959), whereas, when ox growth hormone is added in vitro, glucose uptake is not inhibited and sensitivity to insulin is not reduced. This has led to the view that growth hormone is coverted in vivo to a substance with these properties, or alternatively that another substance is released in vivo under the influence of growth hormone. Experimental evidence has accrued from the studies of Bornstein and Park (1953), Bornstein (1953), Whitney and Young (1957), Vallance-Owen and Lukens (1957), and Krahl et al. (1959). These workers have identified in the plasma of rats or cats a factor which inhibits the effects of insulin (or of serum-albumin which contains insulin) on the uptake of glucose by diaphragm, the presence of which is conditioned by the availability of growth hormone and cortisol (or its analogues).

TABLE IV—EFFECT OF TREATMENT WITH HUMAN GROWTH HORMONE ON THE BIOLOGICAL ACTIVITY OF PROTEIN FRACTIONS FROM HYPOPHYSECTOMISED PATIENTS OR PATIENTS WITH PANHYPOPITUITARISM

Fraction	Subfraction of IV, V, and VI	Glucose uptake (difference from control incubated in buffer alone) mean difference±S.E. of difference (mg. glucose per g. wet diaphragm per hr.)		
		Before H.G.H.	After H.G.H.	Effect of H.G.H.
IV, V, and VI		0·3±0·3	−0·4±0·18	−0·7±0·35
	Albumin + α_1-globulin	0·9±0·37‖	0·3±0·29	−0·6±0·47
	α_2-globulin	0±0·29	−1·0±0·28§	−1·0±0·40
	β-globulin	−0·5±0·32	−0·9±0·27§	−0·4±0·42

For differences marked § P<0·01>0·001, ‖ P<0·05>0·01, and for other differences P>0·05.
For fraction IV, V, and VI the pooled results from one hypophysectomised patient and three patients with panhypopituitarism are given (each difference being derived from means of 18 observations).
For subfractions the pooled results from three patients with panhypopituitarism are given (each difference being derived from means of 12 observations).

Our findings in man are in keeping with these observations in animals, for, whereas H.G.H. does not inhibit the uptake of glucose by diaphragm (table V), it does seem to provoke an inhibitor in plasma when injected into patients. We do not know whether cortisol is also necessary for the formation of the inhibitor which we have identified in human plasma. Whether this inhibitor is formed from growth hormone or released under its influence cannot be decided at present.

Vallance-Owen et al. (1958) have previously identified in albumin fractions of human plasma a factor which is capable of antagonising the effects of insulin on glucose uptake and which is pituitary dependent. Our facto seems to be different in that it is associated with α_2 and β globulin fractions, it inhibits the uptake of glucose in the absence of added insulin, and it is not lost during zone electrophoresis on columns of treated cellulose (cf Vallance-Owen et al 1958) A factor which inhibits the uptake of glucose by diaphragm without added insulin has been identified in the residues of an acid/alcohol extract of human plasma by Baird and Bornstein (1957) We do not know whether this factor is similar to the one detected in our investigation. The physiological and pathological significance of this inhibitor of glucose uptake will only be appreciated when its exact relation to growth hormone, and to the ætiology of diabetes and its complications, has been defined

TABLE V—EFFECT OF HUMAN GROWTH HORMONE ON UPTAKE OF GLUCOSE BY ISOLATED RAT DIAPHRAGM

Concentration of H.G.H. (µg per ml.)	Glucose uptake mean±S.E. (mg glucose per g wet diaphragm per hr)
None	4·1±0·35 (6)
11·5	4·2±0·20 (6)
2·3	3·9±0·23 (6)
0·46	4·3±0·40 (6)

The number of observations is given in parentheses

Our studies have also shown that a protein fraction of human plasma (fraction IV, V, and VI) which inhibits the uptake of glucose by diaphragm may be resolved by further subfractionation into a fraction with demonstrable insulin activity (i e, which stimulates glucose uptake) and fractions containing an inhibitor of glucose uptake This illustrates strikingly how misleading plasma-insulin assays may be when they are based on the effects of untreated plasma on the uptake of glucose by isolated rat diaphragm (cf Randle 1954)

Summary

Protein fractions were prepared from human plasma by a combination of fractional precipitation with ethanol and zone electrophoresis on columns of treated cellulose, and their effect on the uptake of glucose by isolated rat diaphragm in vitro was investigated

Insulin was detected in fractions containing albumin and α_1-globulins, and β-globulins An inhibitor of glucose uptake by diaphragm was detected in α_2 and β globulin fractions of normal human plasma, though not in the corresponding protein fractions of plasma from hypophysectomised patients or patients with panhypopituitarism

Treatment of hypophysectomised or panhypopituitary patients with human growth hormone led to the reappearance of inhibitor activity in α_2 and β globulin fractions

Since growth hormone itself does not inhibit the uptake of glucose by diaphragm, either growth hormone is converted to an inhibitor in vivo or it promotes the release of an inhibitor

We wish to thank Prof F G Young for his interest and encouragement We are greatly indebted to Dr L C Martin of Addenbrooke's Hospital, Cambridge, to Dr R Luft of the Department of Endocrinology, Serafimerlasarettet, Stockholm, to Dr T M Chalmers of the Middlesex Hospital, and to Prof F T G Prunty of St Thomas's Hospital, for samples of blood from hypophysectomised or panhypopituitary patients, to several colleagues for samples of normal human plasma, and to Mrs W Thorne for skilled technical assistance The cost of these investigations was defrayed in part by grants for research expenses (to K W T) from the British Diabetic Association and the Elmore Research Fund, University of Cambridge, and (to P J R.) from the Medical Research Council

References at foot of next column

THE EFFECT OF INTRAGASTRIC OXYGEN ON THE OXYGENATION OF ARTERIAL AND PORTAL BLOOD IN HYPOXIC ANIMALS

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In 1950 Åkerren and Furstenburg claimed favourable effects from the administration of oxygen by gastric tube to anoxic infants, and their work attracted attention in Great Britain although this form of treatment had been advocated earlier by Ylppo (1935) Later Waller and Morris (1953) reported good results using Åkerren and Fürstenberg's technique, and the method has remained popular (e g, Leys 1957) Although Åkerren and Furstenberg quoted data from other sources in support of their procedure, neither they nor the later workers cited above have provided clear quantitative evidence by which to assess its efficacy Moreover full account has not been taken of factors incidental to rather than peculiar to resuscitation by intragastric oxygen in its evaluation.

In 1954, when the possible dangers of overdosage of infants with oxygen were becoming recognised, some work in this laboratory (Banister, Kay, and Coxon 1954) was aimed at developing a means of monitoring oxygen therapy for infants, and in a few experiments (Dr Philip Banister, unpublished) the effects of intragastric oxygen were studied in young kittens Since then various opportunities have arisen for measuring the oxygen saturation in samples of arterial or portal blood of cats and puppies before and after gastric insufflation These experiments were usually designed with some other objective, such as the calibration of oximetric cuvettes (see Kay and Coxon 1957), but for present purposes data have been selected from experiments where other manœuvres were not likely to interfere with the interpretation of the blood-saturation figures

Methods and Materials

Twenty adult cats (males and females), weighing between 2·3 and 4·0 kg, two kittens each weighing 0·75 kg, and two litter-mate male puppies each weighing 4·4 kg were used The animals were anæsthetised with pentobarbitone sodium injected intraperitoneally in a dosage of 40 mg per kg body-weight.

Anoxæmia was generally induced by injecting 0·9% sodium-chloride solution at body temperature into one or both pleural cavities to collapse the underlying lung, occasionally depression of respiration by the anæsthetic sufficed Samples of blood were obtained via a metal cannula inserted into the femoral artery, or through a polyethylene catheter inserted at laparotomy through the splenic vein into the portal vein. The tip

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of the portal catheter was sited headward of the point of entry of the vessels draining the lesser curve of the stomach, and its position was checked by palpation during life and by inspection post mortem

Oxygen was given via a humidifier and warmer, at 0 5–1 0 litre per minute and 100 mm water pressure, through a plastic tube of 4 mm internal diameter which entered the stomach via the mouth In most animals a similar exit tube was also provided, leading into a bubbler which signalled continuity of flow The tips of both entry and exit tubes lay within the body of the stomach

Blood samples were stored in gas-tight syringes at 0°C before analysis for oxygen content and capacity by the manometric method of Van Slyke and Neil (1924)

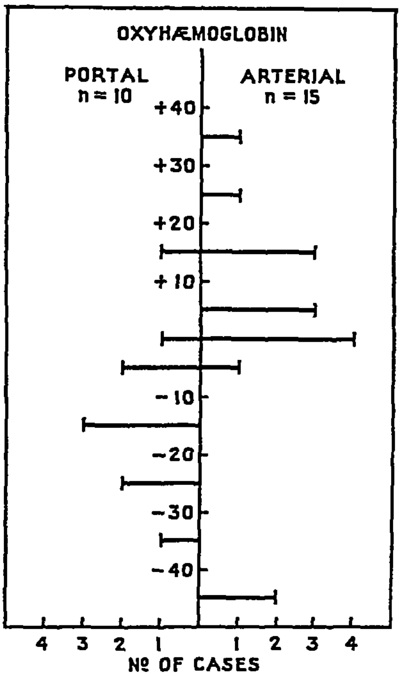

Fig 1—Effect of intragastric oxygen on the hæmoglobin saturation in arterial and portal blood of hypoxic cats

The values on the vertical scale indicate changes in percentage saturation, while the length of the horizontal bars corresponds to the number of cases in which the given change was observed

Observations on arterial blood are plotted to the right of the central axis and observations on portal blood to the left *n*=total number of cases studied

Results

The results for arterial blood, summarised in fig 1, seem at first sight to indicate some rise in hæmoglobin saturation after treatment with gastric oxygen On the other hand, the results for portal blood (also shown in fig 1) reveal in most cases (eight out of ten) a deterioration in oxygenation after treatment But the arterial figures assume a rather different significance when compared, as in fig 2, with the findings when no treatment was given or when air was used instead of oxygen

These experiments suggest that extra oxygen conferred no definite benefit on the animals exposed to it In interpreting figs 1 and 2 it must be noted that the improvement in oxygenation was never limited by full saturation being reached Blood samples were taken at various intervals from 2 to 20 minutes (mean interval 10 minutes) after insufflation was started, but no correlation was found between the duration of treatment with oxygen and improvement in hæmoglobin saturation Of the two kittens studied one showed a considerable fall (28%) and the other a slight rise (12%) in portal oxygenation after treatment

One clear set of data from a puppy are presented in fig 3 This animal was hypoxic as a result of deep anæsthesia with respiratory depression Intragastric oxygen was ineffective in this case, although a very high degree of arterial saturation was maintained by intratracheal oxygen The arterial oxygenation of the other puppy fell slightly (8%) after intragastric oxygen.

Discussion

When Åkerrén and Furstenberg (1950) described the favourable effect of intragastric oxygen in the resuscitation of asphyxiated infants they put forward as a possible explanation a calculation of what amounts to the "diffusing capacity" for oxygen of the infantile gastrointestinal tract Their estimate was based ultimately upon measurements made in two cats by McIver et al (1926), and the justification for including intestinal mucosa in the calculation of the rate of gas absorption after intragastric administration was the radiographic demonstration by Åkerrén et al of extensive gas bubbles in a baby's jejunal and ileal loops Similarly, in the present series of animal experiments, there was frequent abdominal distension (confirmed as being intestinal by direct inspection at laparotomy), and many of the animals passed much flatus during gastric insufflation, even though their oral outflow was completely free Using the data of McIver et al, and making some favourable assumptions, Åkerrén and Furstenberg concluded that oxygen could be transferred across the gut to the portal blood in large enough amounts and rapidly enough to make a significant contribution to the metabolic needs of a hypoxic infant.

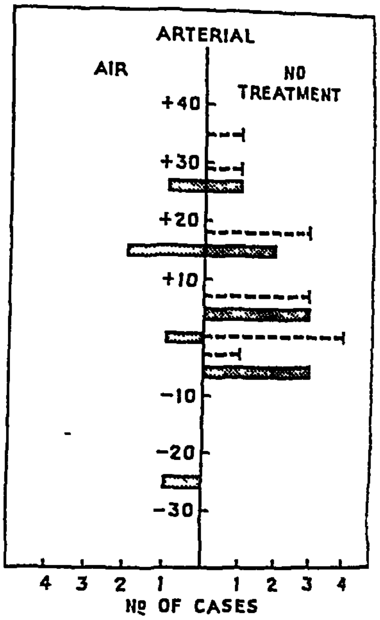

Fig 2—Effect of intragastric air and of simple passage of time ("no treatment") on the arterial hæmoglobin saturation of hypoxic cats

The solid bars indicate the number of cases in which the saturation corresponds to that shown on the vertical scale The interrupted bars reproduce some arterial data from fig 1 for comparison

The average time-lapse in the no treatment cases was 15 minutes and in the air-treated cases 11 minutes

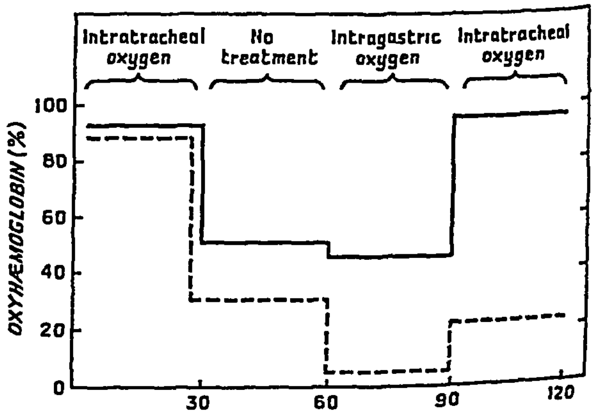

Fig 3—Time course of changes in arterial and portal oxygen saturation in a puppy undergoing various forms of treatment

The solid line represents arterial oxyhæmoglobin as a percentage of the total hæmoglobin, and the interrupted line represents the corresponding values for portal blood

But, although the calculations represented a laudable effort to provide a theoretical basis for Åkerren and Fürstenberg's therapeutic claims, direct evidence of improved portal or arterial oxygenation was not obtained. Later advocates of intragastric oxygen have assessed their results almost exclusively in descriptive rather than quantitative terms One of the few reports traced where actual measurements of hæmoglobin saturation were made was that of the findings of James et al (1959) in a prematurely delivered human fœtus weighing 400 g Here the substitution of intragastric for intrathecal oxygen caused an abrupt fall in aortic saturation, which was rapidly counteracted when intratracheal oxygen was resumed The events in this case thus resembled closely those in the puppy represented in fig 3

Fig 2 shows clearly that, among the anoxic cats in the present series, those which were given intragastric oxygen did not, as a group, display any consistent advantage over the control animals which were not treated or which had insufflation of room air It might be argued that, when improvement appeared to follow intragastric insufflation, this was attributable to reflex stimulation of respiratory movements by the œsophageal tubes, or possibly by stretching of the stomach and adjacent structures, coupled with a high concentration of oxygen in the pharynx from leakage round the tubes Stimulation of respiratory movements by traction on the upper abdominal viscera is recognised (Guedel 1936, Reeve et al. 1951), and, in the laboratory, sustained pressure on the lower sternal region will often promote rhythmical excursions of the chest wall in deeply anæsthetised animals Such factors might well come into play when the stomach is distended with gas, and, if in fact such reflex effects are concerned, intragastric oxygen should be more beneficial in anoxia which is due to depressed activity of the respiratory centre than in that due to pulmonary abnormalities

Some at least of the clinical reports (e g , Waller and Morris 1953) state that cyanosis was seen to disappear after intragastric oxygen was given but before breathing had started This sequence of events is clearly incompatible with the idea that mechanical stimulation of respiratory movement is the primary effect of intragastric oxygen. The remarkable resistance of newborn animals to hypoxia may be relevant in this connection, a puppy on the first day of life may withstand about 40 minutes' exposure to pure nitrogen (Fazekas et al 1941)

The measurements on portal blood (fig 1) are less simply interpreted than the measurements on arterial blood, since a certain amount of surgical trauma was unavoidable in making them At their face value, they suggest that insufflation of oyxgen was more liable to provoke a fall than a rise in portal oxyhæmoglobin This, if real, might be related either to the cooling effect of the gas stream promoting vasoconstriction and stagnation of the blood in the lining of the stomach and intestine, or possibly to venous obstruction resulting from distortion of the regional anatomical relations by distended viscera or the sampling catheter But the gas had been previously warmed and humidified, and placing the tip of the catheter in the main vein caused no gross obstruction of the portal tributaries These findings with regard to portal blood are at variance with those of Poupa et al (1957), who observed an increase of the order of 25% in the oxygenation of portal hæmoglobin after introducing oxygen into the small intestine of rats

In their experiments gas was deliberately excluded from the stomach by ligating the pylorus, and it is said not to have passed beyond the ileocæcal valve, moreover the gas was stationary, and was presumably under pressure greater than atmospheric, although this was not specified Poupa et al described a rise in portal oxyhæmoglobin after insufflation of oxygen, but they found a greater rise after using air, and even a "small and transitory" rise with nitrogen (though from their graph this seems to have been little less than that with oxygen, and air seems to have been rather more effective than oxygen) Direct measurement of the gas absorbed from the intestine in some animals suggested that oxygen disappeared whereas nitrogen did not but the experimental arrangements which these workers used were so different from those in the present studies that inconsistency in the results is not wholly surprising

These laboratory experiments were conducted under such different conditions from those encountered in the management of asphyxia neonatorum that it would clearly be improper to argue from them that clinicians should abandon a resuscitative method which might be beneficial But the intragastric administration of oxygen is not entirely free from risk (Barrie 1959) and misplaced trust in its value may deter the search for more efficacious therapeutic procedures Hence, any quantitative information casting doubt on the value of intragastric oxygen may perhaps incite its advocates to seek more definitive indications of its merits than are at present available

Summary

Changes in the degree of oxygenation of arterial and portal blood were measured after intragastric administration of oxygen to hypoxic animals

The changes resulting from intragastric oxygen were compared with those in the absence of treatment and those when air was substituted for oxygen

Under the conditions of these experiments intragastric oxygen was not beneficial

Thanks are due to Dr R H Kay for allowing the use of data obtained in joint experiments and for his comments, to Mrs A S Spencer, B.SC , and Miss P J Cosgrove for technical assistance, and to Mr A Austin and Mrs O Davenport for help with the figures

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"Given that a community has provided itself with productive scientific resources, its obvious duty is to make the most of them. From time to time issues will arise, sometimes practical, sometimes ethical or moral, sometimes even political The members of the community must take the trouble to inform themselves, or to be informed, of the facts, and they must then decide the issue upon the facts and upon the facts alone, undeterred by the activities of any 'anti' group Because of that leaning to the bizarre which motivates a proportion of the British people, 'anti' groups tend to play a disproportionate part in their decisions, these groups are often wealthy, often dangerously skilled in persuasive propaganda, and—worst of all—sometimes contain people distinguished in some walk of life, who ought to know better"—SIR JAMES LEARMONTH, Surgery and the Community (3rd Maurice Bloch Lecture) Glasgow, 1960

NATURAL HISTORY OF 338 TREATED AND UNTREATED PATIENTS WITH STAPHYLOCOCCAL SEPTICÆMIA

(1936–1955)*

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With a statistical analysis by PAUL WILLIS, PH D , *Statistician, Institute of Agricultural Medicine, State University of Iowa*

BEFORE the discovery of specific treatment, staphylococcal disease accounted for only a small proportion of all infectious disease As new treatments have brought other diseases under control, staphylococcal infection has become relatively commoner Some have suggested that such infection is increasing in frequency (Collins 1956, Finland and Jones 1956, Smith 1958), but others have denied this (McDermott 1956, Hassall and Rountree 1959) Some physicians are pessimistic about the treatment of staphylococcal septicæmia, but recent results of treatment in our hospital have been encouraging

Our experience (Godfrey and Smith 1958) has confirmed that of Finland and Jones (1956) that many of the serious staphylococcal infections in hospitals are acquired after admission

We have carefully assessed the course and outcome of staphylococcal septicæmia with special regard to the onset of the disease and to the effects of treatment

Plan of Study

Our cases were obtained both from the clinical records coded as staphylococcal septicæmia and from the necropsy records of the University Hospitals for the years 1936–55 inclusive These hospitals have 776 beds for the care of indigent patients, and in addition 131 beds for private patients The necropsy-rate in these hospitals has varied between 42% and 72% of all deaths in the twenty-year period Blood-cultures were taken at most necropsies, except those on stillborns and victims of trauma

In the necropsy cases a positive blood-culture was accepted as evidence of septicæmia only if the diagnosis of staphylococcal septicæmia was listed by the pathologist or if focal abscesses or confluent staphylococcal pneumonia were also found Septicæmia was considered to have been present when staphylococcal bacteræmia had been accompanied by major symptoms or signs of infection

Of a total of 73 cases in which single blood-cultures were positive, 6 were rejected as bacteræmia by an independent physician who reviewed their clinical records Of the remaining 67 cases in which single cultures were positive 58% had positive cultures for hæmolytic *Staphylococcus aureus* from sites other than the blood

Age, Sex, and Incidence

Our series consisted of 338 cases of septicæmia, including 69 in which staphylococcal septicæmia developed during another fatal disease These 69 cases will be referred to as cases of "secondary septicæmia" and the others as "primary septicæmia", and all 338 cases as the "combined series"

The sex ratio of males to females was 1 94 to 1, but there was a preponderance of females in the 0–9 and 40–49 age-groups (table I) In half of the large number of men over 70 the disease developed after prostate resection The fatality-rate did not differ significantly between the sexes (75 3% in males and 81 0% in females) In young males the fatality-rate was disproportionately low In the 0–20 age-group the fatality-rate was 46 6% for males, compared with 71 1% for females This difference is statistically significant, yielding a critical ratio of 2 49 with P=0 05 The series included only 3 Negroes

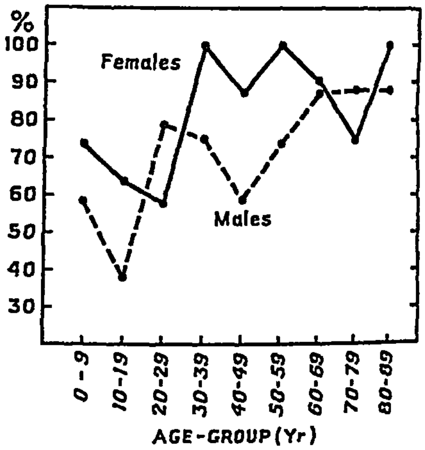

Fig 1—Fatality-rates in patients with primary staphylococcal septicæmia, according to age and sex

The data of table I are shown graphically in fig 1 When least squares best-fit lines are made, the increasing fatality with age in males is statistically significant (P=0 05), whereas in females it is not significant The difference in the two slopes is also not significant

That this is a disease of the extremities of life is clearly shown in fig 2 Patients under 10 and over 69 made up 35 5% of the combined series In other words, 120 cases fall outside the 10–69-year age-group, making a significant fraction of the total (χ^2 27 84 for a P of 0 001)

The overall fatality-rate of the combined series was 77 5%, but, excluding the deaths due to other causes, the corrected fatality-rate for primary staphylococcal septicæmia was 71 7% (table I) Among these cases of

TABLE I—AGE, SEX, AND FATALITY-RATE OF PATIENTS WITH STAPHYLOCOCCAL SEPTICÆMIA

—	Totals	0–9 yr		10–19 yr		20–29 yr		30–39 yr		40–49 yr		50–59 yr		60–69 yr		70–79 yr		80–89 yr	
		M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Combined series No of cases	338	28	37	34	15	20	13	15	4	14	11	29	12	37	14	33	8	13	1
Deaths	262	17	28	14	11	16	8	12	4	9	10	24	12	34	13	30	7	12	1
Primary septicæmia No of cases	269	26	34	32	11	19	12	12	2	12	8	19	9	25	11	25	4	8	1
Deaths	193	15	25	12	7	15	7	9	2	7	7	14	9	22	10	22	3	7	1
Fatality-rate (%)		58	74	38	64	79	58	75	100	58	88	74	100	88	91	88	75	88	100

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* Supported by a grant from the Institute of Allergy and Infectious Disease, U S Public Health Service, no E1011 (C), and by a grant from the Iowa Tuberculosis and Health Association

primary staphylococcal septicæmia, 87 patients received no antimicrobial treatment The death-rate in this group was 89 7%

The annual incidence of staphylococcal septicæmia is shown in table II and fig 3 From 1940 until 1950 there was a fairly steady decline, but thereafter the numbers rose

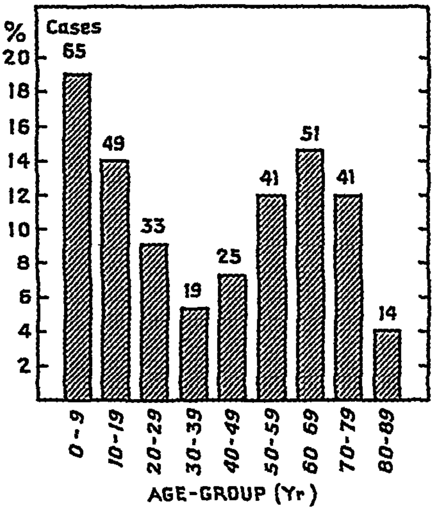

Fig 2.—Age distribution of patients with staphylococcal septicæmia.

If at least squares best-fit line is made, there is no significant downward trend in the overall data, but when the data are analysed for 1936–44, 1945–51, and 1952–55, there is a statistically significant decline in the mortality for the last period

The season of the year when each illness began was noted The months of lowest incidence were July (22 cases), May (23 cases), and August (24 cases), and those of highest incidence were November (34 cases) and January, March, and April (32 cases each month) A χ^2 comparison of the three lowest-frequency months against the three highest yields a significant difference ($P = 0\ 05$)

Bacteriology

All but 5 of the combined series were caused by hæmolytic *Staph aureus* These 5 cases, which satisfied the criteria for the diagnosis of septicæmia due to *Staphylococcus albus*, together with 5 other cases not included here, have been discussed elsewhere (Smith et al 1958a) At least 93% of the cultures taken during life were confirmed at necropsy

At necropsy 14 cases of the combined series had gram-negative rods (proteus, coliforms, or pseudomonas), and 15 cases streptococci and gram-negative rods as well as staphylococci Of 20 cases where there were more than ten cocci per ml, 19 were fatal

In 70 cases diagnosed during life, three or more blood-cultures were taken The first culture was sterile in only 14 cases, of these cases the second culture was positive in 8, the third culture in 5, and the fifth culture in 1

Necropsy Findings

Necropsies were carried out in 327 cases (90 8% of the deaths in the combined series)

The *respiratory system* was the one most commonly involved The most usual lesion was pneumonia Recurring constantly throughout the necropsy reports is the phrase "hæmorrhagic necrotising pneumonia" Empyema was present in only 5 cases (3 were children) in a total of 107 pneumonias, but 3 further cases had sterile pleural effusions 40 cases showed multiple pulmonary abscesses 17 had septic emboli and infarcts of the lungs

Multiple kidney abscesses were the commonest lesions of the *genitourinary tract* (39), and it was hard to separate from these those described as septic infarcts (14) There were 28 instances of pyelonephritis

As regards the *cardiovascular system* there were 26 cases of endocarditis, 7 had rheumatic heart-disease and the others had arteriosclerotic heart-disease Of 19 males and 7 females affected, 2 had infected mural thrombi There was a relatively higher incidence of renal and cerebral lesions in the endocarditis series than in the combined series

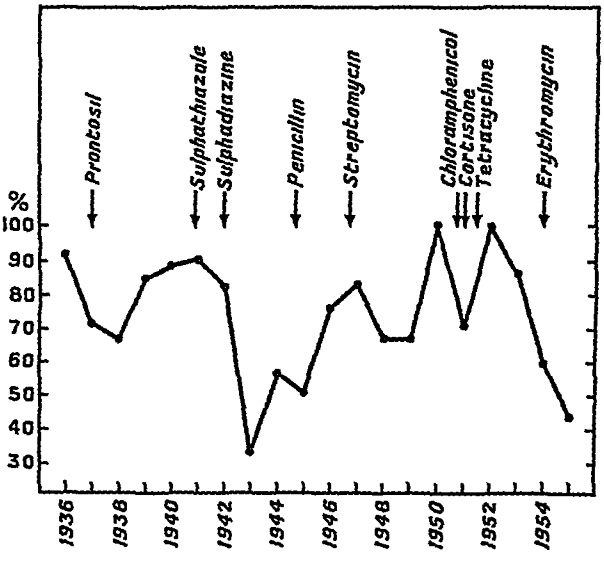

Fig 3—Fatality-rates, from staphylococcal septicæmia, 1936–55

Myocardial abscesses were found in 18 cases, diffuse myocarditis in 2, and pericarditis in 14

The findings in the *gastrointestinal system* included liver abscesses in 12, other abdominal abscesses in 13, peritonitis in 12, and enterocolitis in 9

The findings in the *central nervous system* are incomplete because in 51 cases permission for examination of the

TABLE II—YEARLY INCIDENCE AND FATALITY-RATE OF STAPHYLOCOCCAL SEPTICÆMIA

—	Year 19-																				Totals
	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	
No of admissions	20,888	21,672	20,209	20,888	21,884	23,510	22,562	20,131	18,982	18,672	19,205	19,351	21,327	21,930	19,400	19,358	19,119	19,490	20,145	21,005	
Combined series	12	18	33	26	36	37	12	18	19	12	4	7	8	7	4	11	13	10	26	25	338
Deaths	11	14	23	23	32	34	10	8	11	7	3	6	6	6	4	9	13	9	18	15	262
Primary septicæmia	11	14	29	19	32	30	11	15	18	10	4	6	6	3	2	7	8	7	20	18	270
Deaths	10	10	19	16	28	27	9	5	10	5	3	5	4	2	2	5	8	6	12	8	193
Fatality-rate (%)	91	71	66	84	88	90	82	33	56	50	75	83	67	67	100	71	100	86	60	44	

head was withheld. (In only 3 other cases were there any restrictions on the necropsy.) Meningoencephalitis was the main lesion found in 16 necropsies. There were 12 cases of cerebral abscesses, 3 of cerebral infarction, 2 of cavernous sinus thrombosis, and 1 of massive cerebral hæmorrhage.

There was a great variety of *skin lesions*, of which draining subcutaneous abscesses predominated. Petechiæ were found in 4 cases of endocarditis and also in 2 cases of aplastic anæmia without endocarditis.

Splenic abnormalities noted were "congestion" in 5, and infarction and a septic spleen in 25.

Bone lesions (in cases where these were sought) comprised only one focus in an upper limb, sixteen in the lower limbs, four in the spine, and six in the cranial bones.

Miscellaneous findings.—In a few cases there was destruction of the adrenal glands by necrosis (5) or abscesses (2). In addition to 4 cases of congenital cystic disease the pancreas showed lesions in 21 cases, the common lesion being fatty degeneration (9). Amyloid disease was present in 3 cases.

Lowered Host Resistance

53 of the patients had *malignant tumours*. Their death was probably hastened by the complicating septicæmia. A further 18 patients had *other potentially fatal diseases* such as myocardial infarction, aplastic anæmia, or fungus infection. In this group of 71 moribund patients the infection, which was almost without exception acquired in hospitals, gained entry through the genitourinary tract in 12 and through the respiratory tract certainly in 11 and probably in a further 13.

Diabetes (in 44 cases) we believe was no commoner in the group of patients than in our hospital population, but it was distinctly more common than in the general population (1·5%). There were no patients with recognised *influenza*. We draw particular attention to the frequency of *steroid therapy* (17 cases) as a predisposing cause, this treatment was given in 22·6% of the cases of septicæmia since 1951. The incidence of cases following transurethral resection of the prostate was lower in the second decade covered by the study than in the first. the great majority of such cases occurred before 1943.

These patients with lowered resistance make up 52·7% of the combined series. A miscellaneous group of 82 cases with lowered resistance from other causes included 35 which followed non-urological surgery.

Prognosis Related to Portal of Entry in Primary Septicæmia

The commonest early focus was the skin, the next commonest was the respiratory tract, then the bones and joints, and lastly an operative site. Infections originating in the respiratory tract or following surgery were the most likely to prove fatal. Whether treated or not, osteomyelitis cases proved less malignant than the others, but they did not appear to respond well to treatment. The respiratory tract as a portal of entry was commonest in children under 5 years of age, who made up 41% of this group. Children aged 5–15 years made up 62% of the septicæmias with bone as primary focus.

Among the untreated cases the only significant difference in fatality-rates was that of an unknown focus over a bone and joint focus. In the treated cases the fatality-rate was significantly greater when the disease began in the respiratory tract than when it began in skin, bones or joints, genitourinary tract, central nervous system, ear, or throat, or at an unknown site. Septicæmia originating from surgery or transurethral resection of prostate was significantly more often fatal than septicæmia from an unknown focus or bone and joint.

Duration of Disease in Fatal Cases

22 patients died after only one day or less in hospital, but most of them had a history of septicæmic symptoms for several previous days. Of the 22 patients who died within twenty-four hours after admission, 7 had acute bacterial endocarditis.

Untreated Cases

Of patients admitted before 1941 21% were treated with antimicrobial drugs, whereas subsequently only 21% did *not* receive antimicrobial treatment.

Among the patients not treated with antibiotics the fatality-rate was 85% in 40 who received blood-transfusions, compared with 96% in the remaining 47, this difference is not statistically significant. In the 23 cases not given antibiotics where intravenous glucose was given the fatality-rate was 96%, compared with 88% in the remainder, again the difference is without statistical significance.

In untreated patients the body-temperature, white-blood-cell count, and hæmoglobin did not correlate significantly with fatality.

The relation of fatality to age in untreated primary staphylococcal septicæmia is shown in fig. 4 and compared with similar data in treated cases. The older patients did not spontaneously recover, and the 10–19-year-old group had the lowest death-rate.

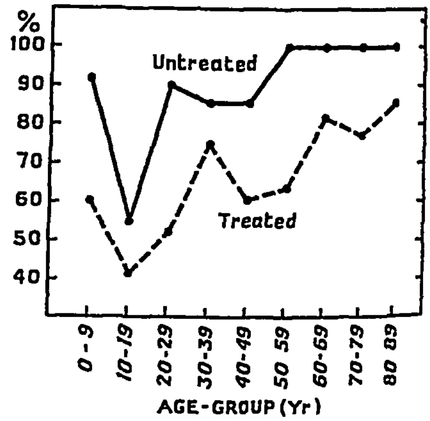

Fig. 4.—Fatality-rates, with and without treatment, in different age-groups from primary staphylococcal septicæmia.

Effect of Treatment

Study of deaths over the twenty-year period (fig. 3) suggests that mortality decreased as each new effective agent came into general use, but that with continued use the new agent lost its efficacy. There is a significant

TABLE III—FATALITY-RATE OF PRIMARY STAPHYLOCOCCAL SEPTICÆMIA WITH DIFFERENT FORMS OF TREATMENT

Treatment	No. of cases	Fatality-rate (%)
1 None	87	69·7
2 Sulphonamide alone	80	77·5
3 Penicillin alone	16	56·3
4 Sulphonamide and penicillin	31	32·3
5 Sulphonamide and penicillin plus*	16	50·0
6 Penicillin and tetracycline plus*	13	69·2
7 Miscellaneous	14	42·9

* Mostly streptomycin.

Treatments	P	*Treatments*	P
(1) v. (2)	0·075	(2) v. (6)	0·465
(1) v. (3)		(3) v. (4)	0·234
(1) v. (4)	0·024†	(3) v. (5)	0·472
(1) v. (5)	0·539	(3) v. (6)	0·479
(1) v. (6)	0·008†	(4) v. (5)	0·295
(2) v. (3)	0·112	(4) v. (6)	0·697
(2) v. (4)	0·719	(5) v. (6)	0·168
(2) v. (5)	0·472		

† Significant = P < 0·05.

TABLE IV—SITE OF ABSCESSES IN 22 CASES OF PYÆMIA

Site	No. of cases	Site	No of cases
Kidneys	20	Abdomen	5
Myocardium	14	Adrenals	3
Lung	13	Bone	2
Brain	10	Subcutaneous	2
Liver	9	Skeletal muscle	2
Spleen	7	Miscellaneous	5
Acute bacterial endocarditis	7		

difference in fatality-rates between 1942 and 1943, and 1952 and 1954, but not between 1947 and 1948, 1951 and 1952, 1952 and 1953, or 1954 and 1955

The results of various treatments singly and in combination are shown in table III and compared with the untreated series The fatality was lower on regimens which contained both penicillin and sulphonamides On each of the treatments there were more recoveries than could be expected on the basis of chance Statistical analysis shows that penicillin alone, sulphonamides and penicillin, sulphonamides and penicillin "plus", and miscellaneous drug regimens were all superior to sulphonamides alone Sulphonamides and penicillin were superior to penicillin and tetracycline "plus" No analysis was made of cases treated in accordance with in-vitro sensitivities

Prognosis of Treated Cases—Body-temperature and anæmia were not significantly correlated with fatality-rates A maximum white-blood-cell count of over 20,000 per c mm was of bad prognostic significance In 51 cases with an abnormal blood-urea-nitrogen the fatality-rate was 82%, and in 26 cases with a normal blood-urea-nitrogen it was 65% In 52 cases this measurement was not recorded.

Pyæmia

22 of the cases had abscesses in three or more organs —notably the kidneys and myocardium with sparing of the lungs (table IV) All age-groups were affected except young adults aged 10–19 4 patients were diabetics and 5 others had serious concomitant disease—namely, lymphoma, ulcerative colitis, actinomycosis, perforated duodenal ulcer, and metastasising adenocarcinoma of the prostate

Of the patients with pyæmia 3 had *Escherichia coli* in their blood, in 3 others *Esch coli* was isolated elsewhere in the body, and 7 others had likely sources of gram-negative bacillary infection, although no such bacteria were isolated These sources included wounds from excision of carcinoma of the vulva and from transurethral resection of prostate, perforated rectum, perinephric abscess, and hæmorrhagic enteritis

Discussion

Apart from a golden age between 1946 and 1950 the incidence of staphylococcal septicæmia was more or less the same throughout the twenty years from 1936 to 1955 It maintained a predilection for males over females in a ratio of 2 to 1 and was particularly common at the extremes of life Our combined series is larger than others because of the care taken by our pathologists in studying necropsies We believe that the incidence of this disease cannot be accurately assessed without bacteriological studies at necropsy 91% (237) of our fatal cases were examined at necropsy This constitutes 2 3% of the necropsies in this period

When staphylococcal septicæmia is borne in mind, the diagnosis is n[illegible] difficult. Fever, disorientation, and dyspnœa are common early symptoms In some cases partial treatment may interfere with diagnosis Tai and Hsieh (1957) found that 92 5% blood-cultures were positive when these are taken before specific treatment and 40 5% were positive when taken afterwards If the organism cannot be isolated from the blood, urine or nasal cultures may prove positive and provide a guide to antibiotic sensitivity

The large number of pulmonary lesions found after death suggests that the respiratory tract may be a common portal of entry, although in only 19% of our cases was this shown certainly to be the portal Many patients receive transoral or transnasal catheter suction, and this may lead to severe pneumonia in nasal carriers of a hospital staphylococcus

In patients with endocarditis staphylococcal septicæmia appears without warning and may begin with neurological symptoms or signs (Dowling et al 1952, Fisher et al 1955), the patient may die within a few days In staphylococcal septicæmia without endocarditis petechiæ were rare, whereas in septicæmia associated with endocarditis they are common (Wilson and Hamburger 1957) Occasionally patients with endocarditis die rapidly, but it is rare for a patient with staphylococcal septicæmia uncomplicated by endocarditis to die rapidly Although treatment must be started early and be guided by clinical experience of the antibiotic sensitivity of prevalent strains, these impressions should be confirmed by in-vitro testing, which must always be done.

The fatality-rate of the untreated cases in the present series corresponds with the rate in other published series (Baker and Shands 1939 [76%], Stookey and Scarpellino 1939 [91 4%], Hamburger and Ruegsegger 1941 [85%], Skinner and Keefer 1941 [82%], McLelland and Goldbloom 1942) The prevalence of hæmorrhagic necrotising pneumonia was striking The time is past when a diagnosis during life or at necropsy of bronchopneumonia or lobar pneumonia is adequate A precise bacteriological or virological diagnosis is essential

Elsewhere (Smith 1956b) we have stressed the importance of host resistance, and so have others (McDermott 1956) The weak strain in a hospital patient who is only clinging to life may do more damage than a virulent strain in a healthy adult Many of these lowered host resistance situations can be demonstrated and studied in mice (Smith and Dubos 1956a, b, and c)

A distressing number of infections were acquired in hospital With the increasing proportion of older people and the increasing number of debilitated persons in the wards of our hospitals, control of infections must be more stringent (Smith 1958) In hospital, patients on adrenal steroids (Shaper and Dysen 1955) and debilitated patients should be watched carefully for signs of developing staphylococcal septicæmia Transurethral resection of the prostate has been a dangerous operation with regard to subsequent septicæmia, but this danger seems to have decreased Our experience agrees with that of others (Baker and Shands 1939, Stookey and Scarpellino 1939, McLelland and Goldbloom 1942) in that cases beginning with osteomyelitis were the least fatal

Sulphonamides in our hands produced no significant improvement in the results of treatment (but see Herell and Brown 1941) Careful choice and use of antibiotics as indicated by in-vitro tests are essential for successful treatment Experience in our hospital since this study was completed suggests that, when a correct diagnosis has been made and the antibiotic sensitivities of the st are known, the fatality-rate need not exceed 25% (Drevets and Smith 1960) Schurger et al (1957) reported a fatality-rate of 34% using appropriate antibiotics Tai and Hsieh (1957) report a fatality-rate of 31 3% in treated patients We have discussed elsewhere the choice of chemotherapeutic agents (Smith 1957, 1958, Flocks et al 1959) Treatment must be continued for at least four weeks Antibiotics are poor weapons against established abscesses, and carefully planned surgery is still an essential part of treatment (Baker and Shands 1939, Tai and Hsieh 1957) As many cocci as possible should be removed mechanically study of the multiplication of staphylococci in mice after inoculation by nine different routes showed that in all instances the mice died when a "critical lethal titre" of staphylococci had been reached no matter in which part of the body the cocci multiplied (Smith et al 1958b)

The severity of cases originating in the respiratory tract or following surgery is evident Others (Tai and Hsieh 1957) have indicated the poor prognosis of cases in coma The number of bacteria per ml of blood cultured is a useful guide to the seriousness of a case (Baker and Shands 1939, McLelland and Goldbloom 1942), and this test should be used more often Young females and old males are particularly liable to die from staphylococcal septicæmia (MacNeal et al 1942) Infections of the respiratory tract are least common in summer and autumn, and mortality from staphylococcal septicæmia is also lowest at these seasons Blood-transfusions do not improve prognosis, and intravenous glucose does not worsen prognosis (as we had thought likely from our studies in mice (Smith and Dubos 1956b) A high white-blood-cell count is an ominous sign (Tai and Hsieh 1957) Anæmia in our series did not affect prognosis, which is contrary to the suggestions of others (Tai and Hsieh 1957). Anæmia in a patient with symptoms and signs suggesting septicæmia should alert the clinician to the possibility of staphylococcal infection The data on treatment show the effectiveness of penicillin alone or with sulphonamides or tetracycline in the period studied This may no longer apply, and precise bacteriological diagnosis and in-vitro assessment of antibiotic sensitivities are essential

Summary

338 cases of staphylococcal septicæmia at a single hospital in the years 1936–55 are reviewed In 69 cases septicæmia developed during another fatal disease The disease occurred in all age-groups, but it was commonest at the extremes of life It affected males twice as frequently as females

Untreated, this disease had a 90% fatality-rate After 1950 the incidence rose, but the fatality-rate in treated cases fell

In the vast majority of instances, the first blood-culture was positive A series of three cultures should suffice for diagnosis A high proportion of cases were not diagnosed before death

At necropsy hæmorrhagic necrotising pneumonia was most often found Endocarditis was found in 10% of the cases with staphylococci in the blood The disease was most likely to prove fatal when staphylococci gained access to the body via the respiratory tract or as a post-operative complication

Many patients succumbed to this disease when they were debilitated by other conditions Administration of penicillin alone or with other drugs was the most effective treatment in the years 1936–55

Our thanks are due to Dr Emory D Warner, professor and head of the department of pathology, for permission to study the pathology records of the University Hospitals, to Dr J Roger Porter, professor and head of the department of bacteriology, for the work in his department on which this study was based, to the staff of the record department, especially Mrs Dolan and Mr William Emanuel, for *their untiring assistance in searching for the many case-histories*, and to Dr William B Bean, Dr Morton Hamburger, and Dr Franklin H Top for their criticism and improvement of our manuscript The errors that remain are our own

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Addendum

Since this paper was written a series of papers on staphylococcal bacteræmia has been published in *Ugeskrift for Læger* (1959, 121, 1593–1614) from the State Serum Institute and the Blegdamshospital in Copenhagen The conclusions are similar to those expressed here

ANTIFIBRINOLYTIC ACTIVITY AND METABOLISM OF Σ-AMINOCAPROIC ACID IN MAN

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IN 1957 workers in Japan found that Σ-amino-*n*-caproic acid (A C A) is a plasmin inhibitor *in vitro* which is useful in inhibiting proteolytic enzymes *in vivo* They gave A C A in doses of 10–20 g per day, by mouth and intravenously, to a hundred and twenty-one patients, and observed no toxic effects They considered that the drug was remarkably effective against emesis gravidarum, dysmenorrhœa, threatened abortion, toxæmia of pregnancy, and various allergic disorders But, although some of these conditions are thought to be associated with increased plasmin activity, no attempt was made to detect fibrinolysis Later Ablondi et al (1959) and Alkjaersig et al (1959) showed that in vitro A C A. acts primarily as a potent inhibitor of plasminogen activation

One of us (I M N) has systematically investigated a large number of clinical coagulation defects In recent years we have found 43 cases with severe fibrinolysis as the cause of hæmorrhagic symptoms Hence we wanted to know whether A C.A would effectively control fibrinolysis in man We therefore studied the effect of A.C.A. on the blood-fibrinolytic system in seven patients, two of whom had pronounced fibrinolysis Since the fate of A.C.A. in the body was not known, we also measured the rate of its disappearance from the plasma, and the amount excreted in the urine

Methods

With the exceptions described below, the methods of collection and preparation of blood, and of measuring the different coagulation factors, were those of Nilsson et al 1957a and b

Assays of Fibrinolytic Activity

Whole-blood-clot lysis—Samples of spontaneously clotted whole blood were incubated at 37°C in a water-bath and the time taken for complete lysis was recorded

Plasma-euglobulin-clot lysis was performed as described by Sherry et al (1959b)

Fibrin-plate method—Fibrinolytic activity was determined on unheated and heated fibrin plates by the methods of Astrup and Mullertz (1952) and Lassen (1952) with modifications Bovine fibrinogen prepared according to the glycine method of Blombäck and Blombäck (1956), with a coagulability of 97–98%, was used in a final concentration of 0 1% in Tris buffer of pH 7 8 and ionic strength 0 15 The fibrin plates were prepared in 'Plexi' glass dishes (diameter 11 8 cm) using 28 ml of the fibrinogen solution, clotted by the addition of thrombin solution (' Topostasine , Roche) 0 2 ml containing 100 N I H units per ml Exactly 0 03 ml of the solution to be tested was added as a drop to the clotted surface Undiluted citrated plasma was usually used, and care was taken that the plasma was added to the plates within 30 minutes of withdrawing the blood We observed considerable decrease in activator and plasmin activity of plasma after freezing or after 1–2 hours' storage at room temperature The plates were incubated for 18–20 hours at 37 C, and the lytic activity was recorded as the product of two perpendicular diameters (sq mm) of the lysed zones (average of three determinations) Because bovine fibrinogen contains plasminogen the lysis recorded on the standard unheated fibrin plates measures the combined activity of plasminogen activator and plasmin in the sample Plasmin alone was measured on heated fibrin plates, where the plasminogen was destroyed by heating to 85°C for 45 minutes The lytic activity (unheated plates) of normal plasma varies between 0 and 70 sq mm

Serum Inhibitors of Plasminogen Activation

Blood was collected in ordinary glass tubes and allowed to clot 2 hours later the serum was separated by centrifugation at 2000 g for 25 minutes, and then stored at −20 C until required The inhibitory effect of serum on plasminogen activation by streptokinase was studied in a clot system of pH 7 4 at 37°C Human fibrinogen ('Kabi') with a coagulability of 95% was used A highly purified streptokinase preparation containing 500 units per µg nitrogen was obtained from Kabi Ltd., Stockholm Each tube contained the following components in order of addition 0 5 ml serum of various concentrations + 0 2 ml of 1% human fibrinogen in Tris buffer of pH 7·4 + 0 1 ml streptokinase solution of various concentrations (50, 100, 200, 300, 400, 500, or 1000 units per ml 0·9% NaCl) + 0·2 ml thrombin solution (10 N I.H units per ml 0 9% NaCl) The lysis-time was determined from when the streptokinase was added Assays conducted at a final streptokinase concentration of 30 units per ml reaction mixture usually showed the differences in inhibitory activity of the serum samples most clearly In each case various concentrations of A C.A were added to the serum collected immediately before administration of A C.A These samples were assayed in the above test system (using a final streptokinase concentration of 30 units per ml) The lysis-times were plotted on a graph, and from this curve the A C.A concentration in the serum samples collected after giving A C.A could be roughly calculated

Determination of A C.A in urine—The method, already described in detail (Sjoerdsma and Hanson 1959), comprised isolation of A.C.A. by high-voltage paper-electrophoresis, development of colour with ninhydrin and copper-spray reagents, elution of the spots from paper, and measurement in a spectrophotometer

Method of A C.A administration—The A.C.A was a commercial preparation from Messrs Light & Co , Colnbrook, Slough, Bucks For intravenous use a 5 or 10% sterile solution of A.C.A in saline was infused over 15–30 minutes Oral doses of A C.A were given as a drink, 6 g being dissolved in 200 ml of mineral water

Clinical Data

The antifibrinolytic effects of A.C.A. were studied in three patients, two (cases 1 and 2) had clinically significant fibrinolysis, and one (case 3) had an increased plasma level of plasminogen activator The metabolism of the drug was studied in four other subjects (cases 4–7)

Case 1—A man of 73, in the terminal stages of hepatic cirrhosis, with ascites, œsophageal varices, and cerebral confusion, had an increased bleeding tendency, and several large hæmatomas The serum-bilirubin was 5 1 mg per 100 ml Increasingly severe fibrinolysis had been observed for a month, during which the fibrinogen value had decreased from 0 16 to 0 04 g per 100 ml

Coagulation studies immediately before A C.A. was given on July 7, 1959, showed coagulation-time, 12 min , bleeding-time, 2 min , platelet-count, 132 000 per c.mm , prothrombin and proconvertin (Owren's P and P), 23%, factor V, 36%, plasma-antihæmophilic-globulin (A H G) activity, 80%, and plasma-hæmophilia-B-factor activity, 14% The plasma-antithrombin activity was increased The fibrinogen was 0 04 g per 100 ml. and the whole-blood-clot lysis-time was 1 hour (normal value >24 hours) The fibrinolytic activity of plasma was 348 sq mm on unheated plates, and 120 sq mm on heated plates The euglobulin-lysis-time was 25 min. The plasminogen + proactivator content of the plasma was 20% of normal, and the inhibitory activity of serum on plasminogen activation was decreased also

After A C.A. was added to the blood, the plasma was assayed

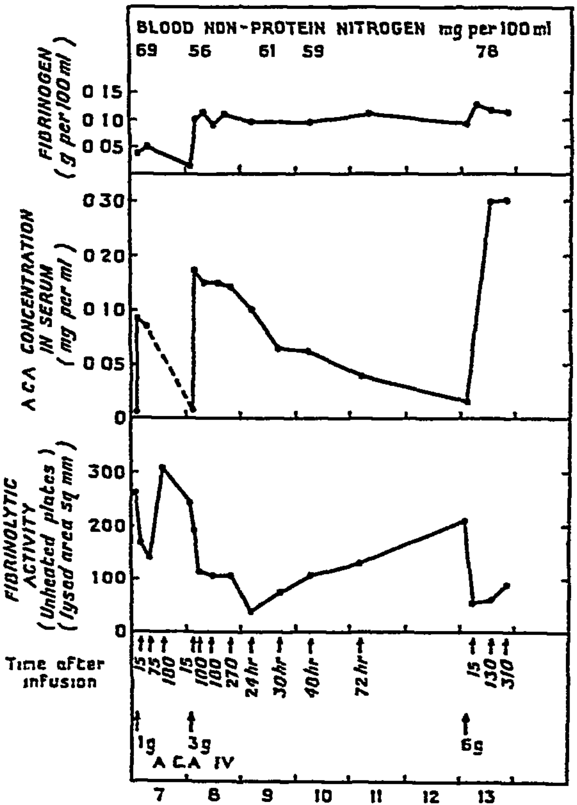

Fig 1—Effect of giving A.C.A. intravenously in case

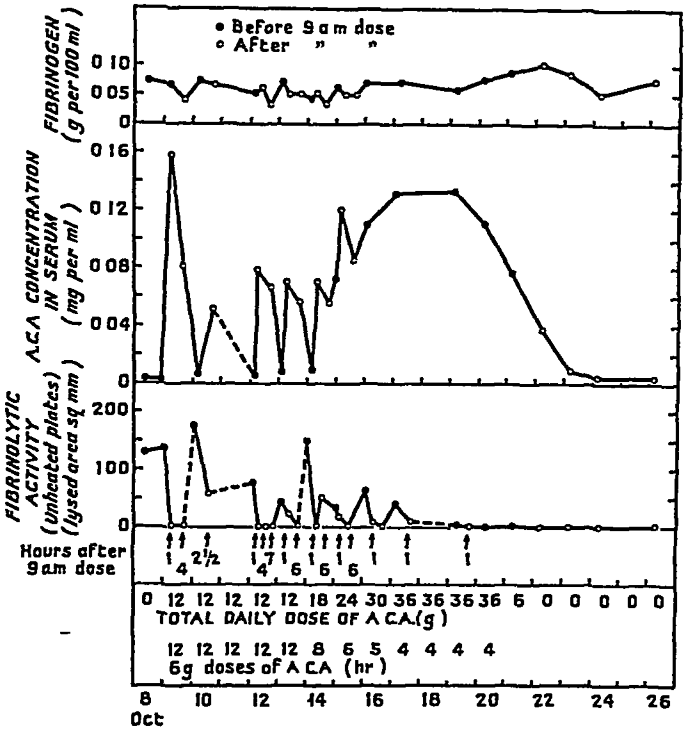

Fig 2—Effect of giving A C.A by mouth in case 2

for fibrinolytic activity on unheated fibrin plates Plasma without A C A. gave a zone of 348 sq mm, while plasma with A C A (0 5 mg per ml blood) gave a zone of 203 sq mm This indicated that both plasmin and activator were present in the patient's plasma

The patient was given A C A intravenously in doses of 1, 3, and 6 g on July 7, 8, and 13 respectively The results of studies on the fibrinolytic system are shown in fig 1 Other coagulation factors were also measured, but no changes were observed In the interval between the second and third doses of A C A the patient went into hepatic coma, and he died on July 14 Necropsy showed hepatic cirrhosis and generalised arteriosclerosis Microscopy of the kidneys did not reveal any abnormality

Case 2.—A man of 61, with acute promyeloblastic leukæmia, had hæmaturia, melæna, and many large hæmatomas on different parts of the body Coagulation studies before A C A was given showed coagulation-time, 10 min, bleeding-time, 24 min, platelet-count, 72,000 per c.mm, prothrombin consumption, 120%, prothrombin and proconvertin (Owren's P and P), 59%, factor V, 44%, plasma-A H G activity, 43%, plasma-hæmophilia-B-factor activity, 70%, and fibrinogen, 0 07 g per 100 ml The whole-blood-clot lysis-time was 15 min, and the euglobulin-lysis-time was 13 min The fibrinolytic activity of plasma was 140 sq mm on unheated plates, and 80 sq mm on heated plates The plasminogen–proactivator content of the plasma was 42% of normal The inhibitory activity of serum on plasminogen activation was decreased

The patient was given A C.A by mouth for 13 days, beginning with a daily dose of 12 g which was successively increased to 36 g (fig 2) When the daily dose of A.C.A reached 24–36 g the hæmaturia and melæna ceased, and the hæmatomas diminished in size and no new ones appeared The results of studies on the fibrinolytic system are given in fig 2 Other coagulation factors were also measured Except that the A H G level increased to 75%, no changes were observed The blood non-protein nitrogen (N P N) was 36 mg per 100 ml before giving A C A, and 90 mg per 100 ml afterwards The leukæmic blood-picture was not affected Despite control of bleeding, the patient's condition deteriorated rapidly, and he died from circulatory insufficiency and bronchopneumonia 6 days after withdrawal of the drug Necropsy showed myeloblastic leukæmia Punctate hæmorrhages were demonstrated in the brain and pericardium The kidneys appeared normal on gross and microscopic examination

Case 3—A woman of 81 with cerebral atherosclerosis and encephalomalacia was confined to bed because of hemiplegia She had no signs of bleeding The blood-N P N was 42 mg per 100 ml Coagulation analyses showed the plasma to have an increased activator activity (lysed zone on unheated plate 290 sq mm, and on heated plate 0), but no whole-blood-clot lysis occurred, and the euglobulin-clot lysis-time was >20 hours The fibrinogen value was 0 66 g per 100 ml, and the other coagulation factors showed normal values The patient was given four intravenous doses of A C A 6 g, and one dose of 3 g, between July 7 and Aug 14, 1959 The subsequent changes were restricted to the fibrinolytic system (fig 3) The blood-N P N value did not increase A month after the last dose of A C A the patient died from bronchopneumonia Postmortem studies, both macroscopic and microscopic, did not reveal any "toxic" changes

Case 4—A 51-year-old woman (weight 51 kg) had psychoneurotic symptoms but no apparent organic disease Investigation of coagulation factors revealed no abnormality The patient was given A C A 6 g intravenously, and 3 days later 6 g by mouth

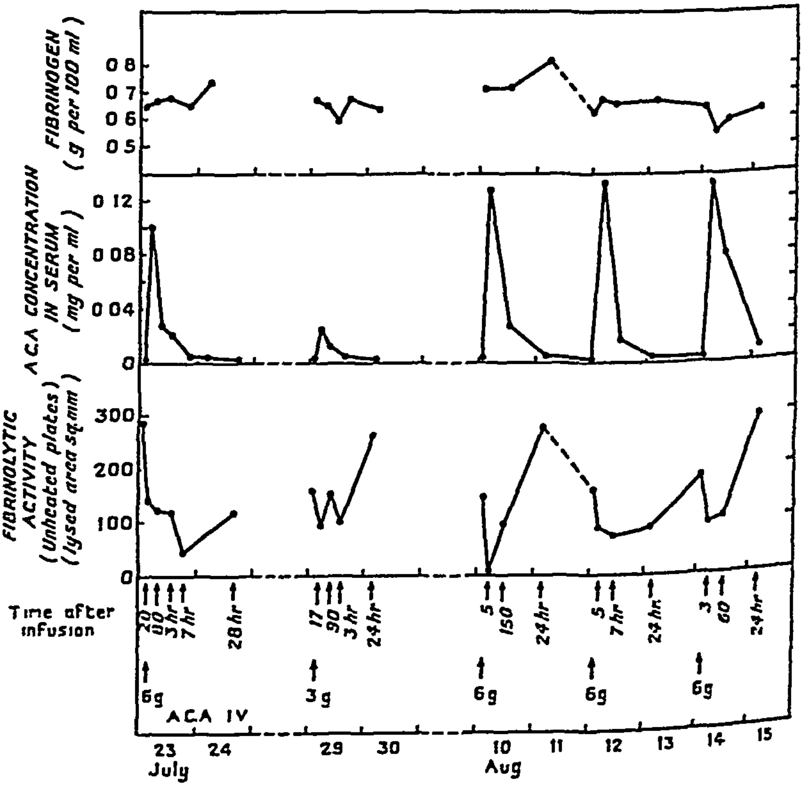

Fig 3—Effect of giving A.C.A intravenously in case 3

SERUM INHIBITOR LEVELS AS A.C.A. EQUIVALENTS (MG. PER ML.) AFTER SINGLE INTRAVENOUS AND ORAL DOSES

Case	Dose (g.)	Route	After A.C.A. (mins.)				
			30	60	120	180	300
4	6	I.V.	0·28		0·02		0·01
	6	Oral	0·10		0·20		0·04
5	6	I.V.		0·12	0·09	0·08	0·06
	6	Oral		0·11	0·12	0·12	0·08
6	6	I.V.		0·12	0·08	0·05	0·02
	6	Oral		0·22	0·19	0·14	0·05
7	6	I.V.	0·14	0·13	0·10	0·08	0·03
	6	Oral	0·14	0·38	0·28	0·19	0·08

I.V. = intravenous.

Cases 5 and 6.—These patients were men of 51 (weight 77 kg.) and 52 (weight 62 kg.). Both had healed peptic ulcers, and their coagulation was normal. They were given A.C.A. 6 g. intravenously, and 6 days later 6 g. by mouth.

Case 7.—A man of 58 (weight 80 kg.) had uncomplicated hypertension and normal coagulation. A.C.A. 6 g. was given intravenously, and 4 days later he had 6 g. by mouth.

Results

The effect of A.C.A. in case 1 is shown in fig. 1.

75 minutes after an intravenous dose of A.C.A. 1 g. the fibrinolytic activity, as measured on unheated fibrin plates, decreased from 250 to 140 sq. mm., and the inhibitory activity of serum, expressed in A.C.A. equivalents, was 0·08 mg. per ml. After 3 hours the fibrinolytic activity and the inhibitory activity of serum had returned to the control values.

Next day the patient was given A.C.A. 3 g. intravenously. As fig. 1 shows this dose was followed by a significant decrease of the plasma-fibrinolytic activity as determined on fibrin plates. The whole-blood lysis-time increased from 1 to 24 hours, and the plasma-euglobulin-clot lysis-time from 25 to 100 min. In addition, the fibrinogen level increased from 0·01 to 0·11 g. per 100 ml. The inhibitory activity of serum was equivalent to 0·18 mg. A.C.A. per ml. This dose was still effective after 24 hours.

During the next 3 days the inhibitory level fell to the original value, and concomitantly the fibrinolytic activity of the plasma increased. The patient was then given a further intravenous dose of A.C.A. 6 g., which again controlled the fibrinolysis and increased the inhibitory activity of serum to a level corresponding to 0·30 mg. A.C.A. per ml. serum. His tendency to hæmatoma formation seemed to diminish. The fibrinogen level increased with treatment from 0·01 to 0·12 g. per 100 ml., and this may be interpreted as a consequence of a longer survival-time of the circulating fibrinogen because of less fibrinolytic activity.

Fig. 2 shows the effect of oral A.C.A. in the patient (case 2) with acute leukæmia and severe bleeding due to fibrinolysis.

One dose of 6 g. caused a significant decrease of fibrinolytic activity as measured on both unheated and heated plates. The effect could be detected as early as 30 minutes after ingestion of the drug. The whole-blood-clot lysis-time ranged between 5 and 12 hours after the drug was given, whereas it had been between 15 and 20 minutes before; corresponding values for the plasma-euglobulin-clot lysis-time were 60 and 13 minutes. The effect of one oral dose of A.C.A. 6 g. lasted for 4–5 hours.

When the inhibitory activity of serum began to decrease to values below 0·06 mg. A.C.A. per ml. the fibrinolytic activity increased. For this reason the oral dose was increased successively in order to keep the inhibitor activity high and the fibrinolytic activity low or negligible. This was not achieved until the total daily dose had reached 36 g., given as 6 g. doses 4-hourly. As can be seen from fig. 2 the fibrinolytic activity then disappeared, and the inhibitory activity in serum remained at 0·1–0·14 mg. per ml. in A.C.A. equivalents. The fibrinogen level only increased from about 0·05 g. per 100 ml. to 0·12 g. per 100 ml. The bleeding symptoms ceased when huge doses of A.C.A. were given, showing clearly that the drug was effective. Altogether, this patient received 282 g. of A.C.A. over 13 days.

Fig. 3 shows the effect of giving A.C.A. intravenously to case 3.

This patient had a high activator content in the plasma, but no plasmin activity. After the first intravenous dose of 6 g. A.C.A. had been given the activator activity decreased from 280 to 50 sq. mm. as measured on unheated fibrin plates. The inhibitory activity in serum reached 1 mg. per ml. A.C.A. equivalents after 20 minutes, and returned to control levels within 7 hours. Three further doses of A.C.A. 6 g. gave similar results.

The overall metabolism of the drug in the body was evaluated by bioassays of "inhibitor" levels in serum and chemical measurements of unchanged drug in the urine. The results of serum assays in four cases after oral and intravenous doses of A.C.A. 6 g. are shown in the table. Where the drug was given by mouth the levels approximated or exceeded those which followed the corresponding intravenous dose in each case. This suggests that absorption from the intestinal tract is rapid and essentially complete. While the data do not permit precise estimation of plasma half-life, it appears to be short—i.e., in the order of 1–2 hours. A large proportion (40–60%) of a single dose of A.C.A. was recovered in the urine within 12 hours, and only a small amount (2–4%) was excreted during the second 12 hours. The values for 12-hour excretion in cases 5 and 6 were 4·9 and 3·9 g. after intravenous administration, and 4·2 and 3·4 g. after oral administration. In case 2, during the 5 days when 6·0 g. of A.C.A. was given every 12 hours, the amount excreted in the urine was 3·8–5·8 g. per 12 hours. The urinary excretion figures also indicate efficient absorption of the drug from the intestinal tract, and show that the primary means of disposal of A.C.A. is by renal excretion.

The patients tolerated the drug remarkably well, even in full dosage. During intravenous infusion no alteration in blood-pressure, pulse-rate, or respiration, and no subjective complaints were encountered.

Discussion

Enhanced fibrinolysis has been reported in various diseases. With the possible exception of abruptio placentæ with defibrination of maternal blood, pathological fibrinolysis (e.g., in carcinoma of prostate, hepatic cirrhosis, leukæmia, obstetric complications, or after pulmonary surgery or extracorporeal circulation) most probably arises from increased circulating levels of plasminogen activator (see reviews by Astrup [1956] and Sherry et al. [1959a]). While the symptoms are often slight (easy bruising, purpura, &c.), and accompanied only by mild hypofibrinogenæmia, patients often present with afibrinogenæmia and severe hæmorrhage which does not respond to the usual therapeutic measures. Fibrinogen, often given in large quantities in these circumstances, is usually without significant effect because of its rapid destruction by plasmin. Theoretically control of fibrinolysis by giving an inhibitor of plasminogen activation followed by the use of fibrinogen should be satisfactory. In these respects, A.C.A. is promising.

A.C.A. temporarily abolished pathological fibrinolysis in cases 1 and 2. The second patient also showed convincing clinical evidence of a therapeutic response during maintenance therapy with A.C.A., for his hæmaturia and melæna ceased. In case 3 great increase in the circulating level of activator in the absence of plasmin activity gave clear evidence of the inhibitory action of A.C.A. on plasminogen activator in vivo.

These studies show that relatively large doses (3–6 g) of A C A are needed to produce an effective level of inhibiting activity in the blood Moreover, although the drug is equally effective whether given by mouth or intravenously, rapid urinary excretion necessitates that, for optimal effects, it must be given every 4–6 hours This is not a deterrent to its use under emergency conditions for a few days Whether more prolonged use of A C A in adequate dosage (20–40 g per day) is safe awaits further evaluation Uræmia is a relative contraindication, in case 1, with an elevated blood-N P N, the effect of A C A lasted longer than it did in the other cases Postmortem examinations in cases 1–3 showed no apparent toxic effects of the drug, but renal function should be watched closely when A C A is given in large dosage for more than a few days

Although A C A seems to represent an important first step, in controlling excessive fibrinolysis it is hoped that more potent drugs with a similar action will be produced

Summary

In short-term studies on two patients Σ-aminocaproic acid was effective in the treatment of pathological fibrinolysis The effect of the drug in inhibiting plasminogen activation was shown in a third patient with increased circulating levels of activator in the absence of detectable plasmin

Metabolic studies indicated efficient absorption of Σ-aminocaproic acid from the intestinal tract, but because of rapid urinary excretion doses of 3–6 g must be given every 4–6 hours for optimal control

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LEPTOSPIRA BRATISLAVA ISOLATED FROM A HEDGEHOG IN SCOTLAND

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Leptospiral infections of hedgehogs have been reported in the U S S R by Ananin (1951, 1954), in Czechoslovakia by Kmety (1954, 1957, 1960), in Poland by Parnas and Dombrowski (1957), and in Roumania by Combiesco et al (1959) Webster (1957) reported evidence of *Leptospira pomona* infections in 2 hedgehogs in New Zealand, and van der Hoeden (1958) described a survey in Israel where 44 of a total of 142 hedgehogs were found to be infected strains of *L canicola*, *L grippotyphosa*, *L m m*, and *L ballum* were isolated

During the spring and summer of 1959 we examined hedgehogs caught in the environs of Edinburgh for evidence of leptospirosis In this survey, which is not yet completed, the kidneys of 1 hedgehog were found to harbour a strain of leptospire which is apparently identical with *L bratislava*, the serotype which is most commonly found in hedgehogs in Czechoslovakia and which also occurs in these animals in the U S S R. and Poland

Materials and Methods

The hedgehog (*Erinaceus europæus europæus*, Linnæus) was brought to the laboratory alive and was killed with chloroform. Heart-blood was withdrawn immediately for agglutination tests, and a specimen of urine was obtained from the bladder The kidneys, which appeared swollen and darker than normal, were removed, and, after the surface had been seared with a hot scalpel blade, small particles were punched out with a Pasteur pipette and introduced into bottles of modified Stuart's medium (Bryan 1957) Two of the bottles were incubated at 37°C and two at 28°C

Results

No leptospires were seen in the urine when it was examined by dark-ground microscopy

The hedgehog serum gave the following results when tested against seven leptospiral serotypes (results expressed as the reciprocals of agglutination titres) *L icterohæmorrhagiæ* 30, *L canicola* negative, *L pomona* 30, *L grippotyphosa* 30, *L sejroe* 100, *L bataviæ* 100, *L ballum* 30

One of two kidney cultures incubated at 37°C was positive eleven days later The strain was labelled " strain hedgehog 10 "

Strain hedgehog 10 was not agglutinated by the hedgehog serum It reacted to full titre with antisera *L australis A* and *L muenchen*, and there was also a high cross-reaction with *L autumnalis* antiserum, which suggested a somewhat closer affinity with *L muenchen* However agglutinin-absorption tests showed that strain hedgehog 10 was neither *L australis A* nor *L muenchen* The results are shown in the accompanying table

ABSORPTION TESTS WITH STRAIN HEDGEHOG NO 10

Antiserum	—	Titre against		
		L australis A	*L muenchen*	Strain no 10
australis A	Unabsorbed	10,000	3000	3000
	Absorbed *muenchen*	3000	−ve*	−ve
	Absorbed strain no 10	3000	300	−ve
muenchen	Unabsorbed	1000	3000	3000
	Absorbed *australis A*	−ve	3000	3000
	Absorbed strain no 10	100	3000	−ve
Strain no 10	Unabsorbed	300	1000	10 000
	Absorbed *australis A*	−ve	100	3000
	Absorbed *muenchen*	−ve	−ve	3000

* No agglutinin in dilutions of 1/50 upwards

At this stage of identification the strain was sent to Dr Emil Kmety, of Bratislava, who has carried out antigenic analysis of many strains related to *L australis A* and has found that they can be differentiated into serotypes which together form an australis A group (This work, reported in Lublin, Poland, in 1958, is in process of publication) Kmety found by cross-absorption tests that our strain " hedgehog 10 " was identical with the serotype *L bratislava* of the australis A group

Comment

Kmety (1960) reports that the first strains of leptospires isolated from hedgehogs, *Erinaceus europæus roumanicus*, in Slovakia in 1953 were found to form a new serotype within the australis A group It was named *L bratislava*

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* Dr Broom died on March 16

Later strains referred to as *L erinacei europaei* isolated by Ananin (1954) in the U S S.R and by Parnas et al (1958) in Poland were found to be identical with *L bratislava* In his survey of hedgehogs in Slovakia, Kmety found that 14 of 17 strains of leptospires isolated from the kidneys were identifiable as *L bratislava* and that 35 4% of the hedgehog sera gave positive agglutination with that serotype with titres ranging from 1 in 100 to 1 in 50,000 It appears therefore that the hedgehog is the main host for *L bratislava* in Eastern Europe In a personal communication Kmety states that this strain has only once been isolated from another animal—viz, *Clethrionomys glareolus* (bank vole)—and once from the blood of a patient

It is interesting that an identical organism has been found in a hedgehog in this country A continuation of the survey will reveal to what extent hedgehogs carry this particular organism How the infection was introduced it is difficult to say Possibly the new serotype has emerged independently in both localities through adaptation to the hedgehog of strains of leptospires derived from other animal sources (Gsell 1949)

Until recently only *L icterohæmorrhagiæ* and *L canicola* had been identified in this country, but Broom and Coghlan (1958) showed that wild rodents were carrying other serotypes—viz, *L ballum* and strains related to *L saxkoebing* and *L sejroe* Another serotype can now be added to the list

The fact that no antibodies for strain hedgehog 10 could be detected in the hedgehog serum is noteworthy Similar observations were made during the rodent survey (Broom and Coghlan 1958) when mice harbouring leptospires in their kidneys were found to be negative in serological tests Van der Hoeden (1958) reported only low serum titres for the homologous organisms in some hedgehogs from which leptospires were isolated, and in 1 hedgehog carrier of *L ballum* no antibodies either for the homologous strain or for 16 other serotypes were found These findings re-emphasise the importance of not drawing unwarranted conclusions regarding the prevalence of leptospirosis from surveys based on serological tests alone

Summary

The first isolation of *Leptospira bratislava* in Britain is reported It was cultured from the kidneys of a hedgehog caught near Edinburgh This organism, which is closely related to *L australis A*, is the type most commonly found in hedgehogs in Czechoslovakia

I wish to thank Prof J W Wolff, of the W H.O /F.A.O Leptospirosis Reference Laboratory, Royal Tropical Institute, Amsterdam, to whom I wrote for advice regarding the correct taxonomic placing of the hedgehog strain Professor Wolff states that, although exact data of the serological investigation of "*L bratislava*" have not yet been published, he believes, from the work already done, that the strain will ultimately be recognised officially as a distinct serotype.—J D C

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Preliminary Communication

LYSOKINASE ACTIVITY IN ASCITIC FLUID

A PROTEOLYTIC enzyme capable of fibrinolysis occurs in normal blood as an inactive precursor, plasminogen, which is associated with the globulin fraction An inhibitor, antiplasmin, is present in excess in the albumin fraction Plasmin not only produces fibrinolysis but also digests other plasma-proteins, including fibrinogen.

The modes of activation of plasminogen are debatable, but for convenience in this communication, we use what Astrup [1] called the "activation scheme of 1954" (fig 1)

Plasminogen can readily be activated in vitro by chloroform, which destroys antiplasmin, by techniques, such as fractionation of the plasma, which separate the plasmin-antiplasmin complex, and by the direct action of trypsin and of a tissue activator (fibrinokinase) Activation in vitro may also be achieved by streptokinase which converts a proactivator in the plasma to an activator, which in turn reacts with plasminogen to form plasmin

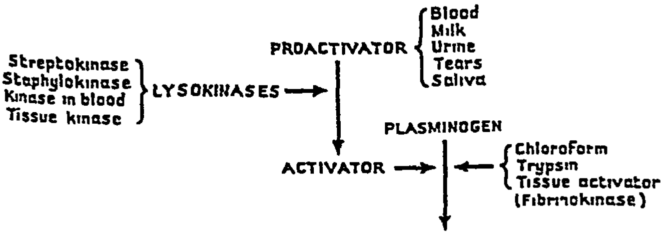

Fig 1—Astrup's activation scheme of 1954.

Activation of plasminogen in vivo—which is referred to as spontaneous fibrinolysis—is highly complex, but in essence a proactivator present in the plasma is converted to an activator which, after clotting [2] converts plasminogen to plasmin The way proactivator is converted to activator is unknown The evidence for the existence of lysokinase is slender A serum-lysokinase may be present in human and dog blood [3,4] Attempts have been made to isolate active lysokinase from animal (including human) tissues, but in few instances have extracts shown measurable quantities of an agent with a lysokinase effect.[1]

In man [5-8] fibrinolytic activity can be induced within subcutaneous veins and arteries The effectors have not been identified, nor is it known how they activate the fibrinolytic system in plasma Efforts to determine the nature of the factor secreted have been thwarted by difficulties in isolating lysokinase and by lack of knowledge of its action, for lysokinase, according to the scheme presented above, might well be the factor We knew that stimulation of veins seemed, at first sight, to produce two forms of fibrinolytic activity One was very labile and required for its demonstration a low-temperature technique first used by Fearnley et al [9] The other was relatively more stable, being due to an activator in the plasma By a happy chance, while investigating antiactivator activity in hepatocarcinoma,[10] we found a rich source of what seems to be lysokinase

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[1] Astrup, T *Blood*, 1956, 11, 781

[2] Mullertz, S *Proc Soc exp Biol N Y* 1956 82, 291

[3] Lewis, J H, Ferguson, J H *ibid* 1951, 78, 181

[4] Mullertz, S International Conference on Thrombosis and Embolism p 79 Basle 1955

[5] Kwaan, H C, McFadzean A J S *Clin Sci* 1956 15 245

[6] Kwaan, H C, Lo R, McFadzean A J S *ibid* 1957 16, 241

[7] Kwaan, H C, Lo, R, McFadzean A J S *ibid* p 255

[8] Lo, R, McFadzean, A J S *ibid* 1958 17, 499

[9] Fearnley, G R, Revill R Tweed, J M. *ibid* 1952, 11, 30

MATERIAL AND METHODS

The supernatant of centrifuged blood-free ascitic fluid from abdominal paracentesis was used With the exception numbered 12 below, the ascites had developed in seven patients with hepatocarcinoma complicating cirrhosis of the liver Where appropriate, clotting was produced by adding 0 1 ml of a solution of bovine thrombin (20 units per ml) to the test system, which was observed frequently so that the time of complete lysis was noted Other methods are more appropriately described below

RESULTS

1 Ascitic fluid, 0 5 ml, was mixed with 0 5 ml of citrated normal human plasma in a water-bath at 37°C, and the mixture clotted All clots lysed The mean lysis-time was 1 5±0 4 hours

2 To determine whether ascitic fluid contained plasmin, specimens of such fluid were applied to heated fibrin plates[11] The fibrin was never affected Lack of effect upon fibrinogen, casein, and gelatine provided additional evidence that plasmin was absent

3 To exclude the possibility that ascitic fluid might contain plasminogen attempts were made to prepare chloroform-activated plasmin by the method of Rocha e Silva and Rimington,[12] as modified by Bidwell[13] No plasmin activity could be detected in any specimen prepared

4 Since bovine plasma contains very little, if any, proactivator the effect was tried of various amounts of ascitic fluid upon bovine plasma No lysis was seen in any specimen in concentrations of ascitic fluid/bovine plasma ranging from 1/1 to 20/1 Hence we concluded that ascitic fluid contains neither activator, which converts plasminogen to plasmin after clotting, nor tissue activator, which converts plasminogen to plasmin directly

5 To determine whether ascitic fluid contained proactivator or inactivated activator, 50 units of streptokinase in 0 5 ml of saline were added to mixtures containing various amounts of ascitic fluid and bovine plasma The ascitic fluid/bovine plasma ratio ranged from 1/1 to 20/1 In five specimens no lysis occurred The other two underwent lysis when the ratio ascitic fluid/bovine plasma was 10/1 or more These two exceptions were dropped from the succeeding observations

6 The addition of human plasma in appropriate amounts, with its content of proactivator, to mixtures of ascitic fluid and bovine plasma resulted in lysis of the clot formed when thrombin was added In the light of the scheme of activation set out above, the most reasonable interpretation is that the ascitic fluid has lysokinase activity

7 Specimens of ascitic fluid were incubated at 37°C, 0 5 ml samples were removed at intervals and mixed with 0 5 ml of plasma, clotted, and watched for lysis Fig 2 shows the results

8 To determine whether the addition of ascitic fluid to ice-cold plasma augmented the subsequent rate of lysis of the clotted mixture, 0 5 ml samples of fresh ascitic fluid were mixed with 0 5 ml of plasma in an ice-bath (A) or with 0 5 ml of plasma at 37°C (B) Thrombin was then added to both tubes, and that in the ice-bath was transferred to the water-bath at 37°C The mean lysis-time of A was 56±2 6% more rapid than that of B

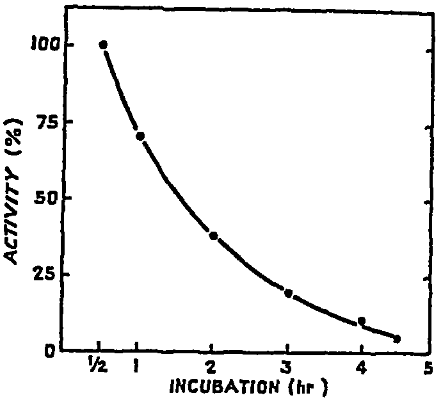

Fig 2—Loss of lysokinase activity on incubating ascitic fluid at 37 C. 100% activity is that estimated 30 minutes after withdrawal of the ascitic fluid

9 Ascitic fluid was concentrated by dialysis in a refrigerator at 2°C While the activity of the dialysate in activating the fibrinolytic system in undiluted human plasma was greater, volume for volume, than that of the undialysed ascitic fluid, it was significantly less than was expected, indicating that, despite the low temperature, considerable activity had been lost

10. Ascitic fluid dialysed as above was subjected to paper electrophoresis at 2°C, and eluates of the protein fractions were prepared using saline buffered to pH7 4 In two of five instances, when the eluate of the γ-globulin fraction was added to undiluted human plasma, the clot underwent lysis when thrombin was added Addition of eluates of the other fractions had no lytic effect

11 The observations numbered 7 and 8 suggested the presence of an antilysokinase in ascitic fluid and in plasma Eluates of ascitic fluid were prepared as above and tested for antilysokinase activity Ascitic fluid, 0 5 ml, was mixed with the eluate of the fraction under test, and allowed to stand in the water-bath at 37°C for 5 minutes Plasma, 0 5 ml, was then added, and the mixture was clotted by thrombin As a control the observations were repeated substituting buffered saline for the eluates Eluates of the β-globulin fraction alone were active and had a striking inhibitory effect, but this was greatly reduced if the reagents were kept in an ice-bath before thrombin was added

12 To find a more readily available source of activity observations were made on ascitic fluid from five patients with cirrhosis of the liver The mean lysis-time of clotted mixtures of equal parts of ascitic fluid and plasma was 8 4±1 hours, which is significantly less rapid ($P = < 0 001$) than that encountered in hepatocarcinoma But, on the other hand, when streptokinase was added to mixtures of ascitic fluid and bovine plasma, one or more of the clotted mixtures lysed, although the ratio ascitic fluid/bovine plasma at which lysis occurred varied greatly This finding is consistent with the presence of significant quantities of proactivator or inactivated activator, and we therefore temporarily abandoned our observations on ascitic fluid in cirrhosis

COMMENT

It seems reasonable to conclude that a factor in the ascitic fluid associated with hepatocarcinoma (probably in the γ-globulin fraction) has lysokinase activity, and that the β-globulin fraction of ascitic fluid has antilysokinase activity. The rapid loss of lysokinase activity on incubation of ascitic fluid at 37°C indicates that, in vivo within the peritoneal cavity, lysokinase is continuously produced and destroyed. The source of lysokinase is unknown, but we have a promising lead in that a watery extract of the sediment of centrifuged ascitic fluid was found to be active. The source of antilysokinase seems to be the plasma; we have evidence that it is present in the β-globulin fraction, and that it may be β-lipoprotein.

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[10] Kwaan, H C, Lo R, McFadzean, A J S ibid 1959, 18, 252

[11] Astrup, T, Mullertz, S Arch Biochem 1952, 40, 346

[12] Rocha e Silva M Rimington C. Biochem J 1948, 43, 163

[13] Bidwell, E ibid 1953, 55, 497

The finding of proactivator or inactivated activator in the presence of lysokinase activity in two of the seven patients with hepatocarcinoma seems at first to be contradictory. This has also been encountered in streptokinase-activated human plasma, and it is discussed ably by Mullertz.[14]

The augmentation of fibrinolysis when mixtures of ascitic fluid and human plasma are clotted at low temperatures suggests that antilysokinase activity is reduced at low temperatures. This raises the possibility that the labile fibrinolytic activity encountered on stimulating veins, which is demonstrable by the low-temperature technique, may well represent the action of lysokinase which, at higher temperatures, would be at least partly inhibited. The more stable fibrinolytic activity, due to the activator, represents the action of lysokinase which has not been so inhibited. This possibility is supported by the finding of Greig and Runde[15] that in lipæmic plasma the β-lipoprotein fraction exerts an inhibitory effect upon labile fibrinolytic activity.

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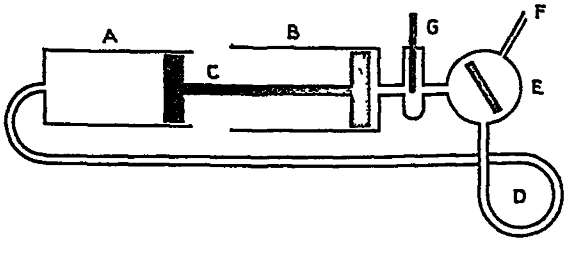
New Inventions

A DEVICE FOR CONTINUOUS MEASUREMENT AND RECORDING OF INTRAVASCULAR pH

We have devised an instrument which allows the continuous measurement and recording of intravascular pH at constant temperature. The advantages over previous techniques[1] are: only semimicro quantities of blood are required, the subject need not be heparinised, and protein deposition on the glass electrode system does not seem to be troublesome.

The chemistry of the technique is based on observations by Hastings and Sendroy[2] and Van Slyke et al.[3] These workers found that, when blood was diluted 1:10 with neutral saline solution, the pH of the diluted blood was that of the original sample. The method was used for the spectrophotometric determination of pH of body fluids with phenol-red indicator.[3 4] Our instrument dilutes and mixes blood with neutralised saline in the proportions 1:10, and the pH of the diluted blood is measured in a microflow electrode system at a predetermined and constant temperature.

The mixing of blood and saline in fixed proportions is achieved by means of a special pump (see figure). Two 'Perspex' cylinders, A and B, are fitted with pistons having a common connecting rod C, which is screw-threaded. The connecting rod is driven by a worm-reduction unit without rotation of the pistons. The internal diameter of cylinder A is 2.00 in. and that of B is 2.10 in., thus the volumes displaced are in the ratio 10:11. Neutral heparinised saline from cylinder A is delivered through a heat-exchanger D, to a small perspex mixing chamber E, which contains a polythene-coated iron rod driven by a rotating magnet. Blood enters the mixing chamber via a short polyethylene catheter F, and the diluted suspension leaves the mixing chamber and enters the microflow glass-electrode system G (Electronic Instruments Ltd., type SMF 23) from which it passes to the cylinder B. The glass-electrode system, reference electrode, and potassium-chloride bridge, together with the heat-exchanger D, are immersed in a water-bath maintained at 38°C.



Neutral saline is prepared as described by Van Slyke et al.[3] with the addition of heparin 10 i.u. per ml. The cylinder A and the dead space of the components B, D, E, and G, are filled with neutral heparinised saline. A sterile catheter is inserted into an artery or vein, and the magnetic stirrer is set in motion. Pumping is then started, and when diluted blood enters the electrode system, pH readings are taken. The pH is determined by a 'Vibron' measuring unit, and an electrometer having high sensitivity and stability (Electronic Instruments Ltd., models c33B and 33B). The instrument is calibrated by phosphate buffers as described by Van Slyke et al.,[3] the pH of these being periodically checked against phthalate and borate standards.

The output from the electrometer is fed to a pen galvanometer (Record Electrical Company Ltd., Altrincham, Cheshire), which records the pH on moving paper. The laboratory-made recorder is fitted with other pen galvanometers (Associated Electrical Industries Ltd., London), which enable simultaneous electrocardiographic, electroencephalographic, and blood-pressure tracings to be made.

The validity and accuracy of the method has been assessed by measurements on blood samples equilibrated at 38° C and at known gas tensions. Experiments on the anæsthetised dog have shown that the device gives an accurate continuous assessment of the intravascular pH. For ordinary purposes, the flow-rate is adjusted to about 0.1 ml. of blood per minute, but, when very rapid changes in blood pH are expected, the rate is increased to avoid error due to the time-lag inherent in the dead space of the components E, F, and G. The results during anæsthesia and other conditions will later be described in detail.

We wish to thank our engineering colleagues and Messrs. Denholm, Rees & O'Donnell of Liverpool for constructing the pump unit. The work was supported by grants from the United Liverpool Hospitals research committee.

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[1] Aschberg, S., Sonderlund, S., Tunell, R. *Scand. J. clin. Lab. Invest.* 1959, 11, 114.

[2] Hastings, A. B., Sendroy, J. *J. biol. Chem.* 1924, 61, 695.

[3] Van Slyke, D. D., Weisiger, J. R., Van Slyke, K. K. *ibid.* 1949, 179, 743.

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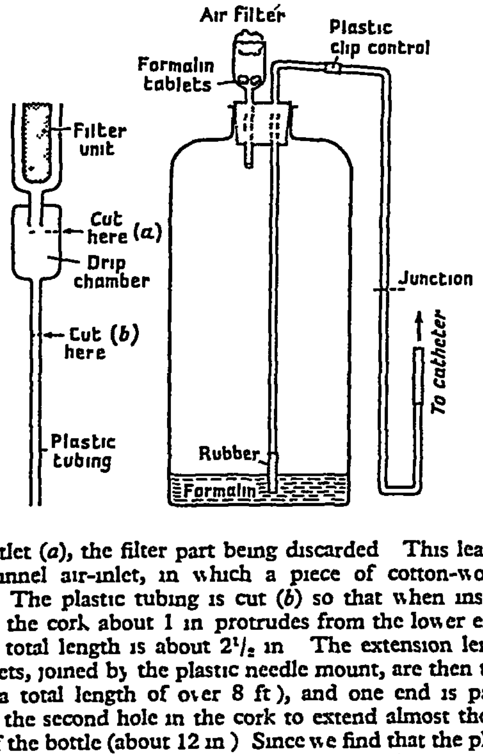
DISPOSABLE CLOSED DRAINAGE SETS IN UROLOGY

Closed drainage as a means of preventing infection in urological disorders—particularly those due to prostatic enlargement—has become well established [1,2] Consequently a considerable load has been placed on theatre and sterilising staff in preparing, sterilising, cleansing, and resterilising apparatus Hence we thought that time, trouble, and expense would be saved if the plastic transfusion sets used throughout much of the country could be adapted for closed urological drainage instead of being discarded Our experience has been comparatively brief, but colleagues elsewhere have urged us to make our suggestions known

In essence the requirements are

1. Bottles of up to 2 5 litres capacity (commercial Winchester)
2. Bark corks to fit these bottles
3. Discarded transfusion sets which have been washed through with cold tapwater (two required for each outfit)
4. A cork-borer no 2
5. A sharp knife or razor blade
6. *Sterilisable heat-sealing and non-sealing* '*Cellophane*', as used throughout the Blood Transfusion Service
7. Formaldehyde solution *B P*
8. Paraformaldehyde tablets 1 g (we have used 'Formogene')

As shown in the figure the cork is drilled in two places The drip chamber to the transfusion set is cut off at the level of the filter outlet (*a*), the filter part being discarded This leaves a small funnel air-inlet, in which a piece of cotton-wool is placed The plastic tubing is cut (*b*) so that when inserted through the cork about 1 in protrudes from the lower end—i e, the total length is about $2^1/_2$ in The extension lengths of two sets, joined by the plastic needle mount, are then taken (giving a total length of over 8 ft), and one end is passed through the second hole in the cork to extend almost the full depth of the bottle (about 12 in) Since we find that the plastic tubing end is inclined to curl up, we add a rubber connector to give added weight A second rubber connector on the proximal end enables it to be attached to the catheter An ordinary plastic clip is placed close to the cork so that drainage can be restricted if necessary The apparatus, now ready for sterilising (and to do this successfully the plastic tubing must be coiled in such a way that it does not kink), is wrapped in non-sealing cellophane and then in heat-sealing cellophane For convenience we place two sets in each packet They are sterilised in the autoclave at 15 lb pressure for 30 minutes (without apparent deterioration of the plastic), and dried by drawing a vacuum in the ordinary way The bottles are plugged with cotton wool, covered with greaseproof paper, and also sterilised in the autoclave



Before use 100–150 ml of formaldehyde solution is placed in the bottle, and the cork and tubing are attached, the long tube being manipulated inside the bottle so that its end is below the surface of the liquid A tablet of paraformaldehyde is put in the funnel air-inlet, and the open end of the long tube is attached to a glass tube placed in the catheter The apparatus is now ready for use, but beforehand it is essential to check (1) that the clip is in the open position, and (2) that no serious kink is present (About 1 in 40 of our sets has kinked in sterilisation, but this can be further reduced with practice)

In our hands the set, including the bottle, has been replaced when the bottle has become full, not less often than once per day We leave instructions that if a set becomes blocked by clot or debris no attempt should be made to clear it, but a fresh set should be used In practice blockage seldom occurs

A specimen of urine can be obtained without disconnection by shutting off the clip for a few minutes and then withdrawing urine through the rubber connector at the point of attachment to the catheter by means of a syringe and needle Providing standard bottles are used, the output of urine can be measured by attaching a volume indicator as described by Miller et al.[1]

Wider adoption of our proposals would, we believe, help to reduce the incidence of bladder infection The equipment is simple to prepare, and the basic requirements cost virtually nothing

We are indebted to Dr S Vakil and Sister D M Courage, both of the Dorset County Hospital, for helpful and constructive criticism, and to Dr G H Tovey, regional transfusion director, Southmead Hospital, Bristol, for urging us to write this account

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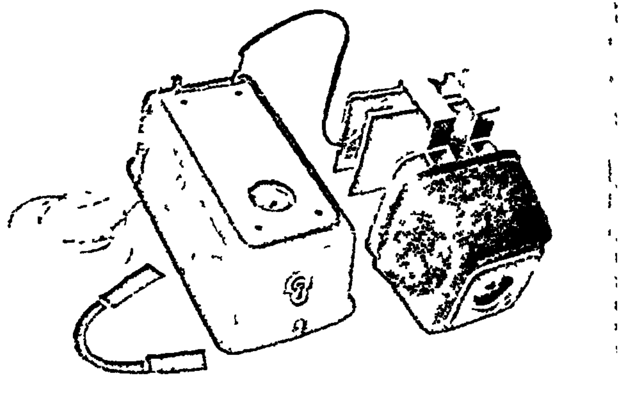
AN ELECTRONIC NEONATAL RESPIRATORY MONITOR

Apnœic attacks are common in the neonatal period and are a frequent immediate cause of death particularly in premature babies, in babies with cerebral irritation, and in babies with any form of respiratory difficulty As their early detection is of the utmost importance, a special nurse is sometimes delegated to watch respiration However, such special nurses are not always available, and their services are costly in terms both of cash and of time The respiratory monitor is intended to replace the special nurse and to summon an attendant as soon as an apnœic attack occurs During a six-month trial it has proved efficient and reliable, and on several occasions it has warned a special nurse, watching the baby, of a cyanotic attack of which she was unaware

A detector is strapped across the upper part of the baby's abdomen and is connected to a transistorised circuit, controlling an alarm hooter The circuit, batteries, and hooter are contained in a case 4 × 4 × 9 in To avoid false alarms caused by periodic breathing, the circuit is so designed that the alarm does



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[1] Miller, A, Gillespie, W A, Linton, K B, Slade, N, Mitchell, J P *Lancet*, 1958, ii, 608

[2] Miller, A, Linton, K B, Gillespie, W A, Slade, N, Mitchell, J P *ibid* Feb 6, 1960, p 310

not sound for 15 seconds after the start of apnœa As an attendant is not always present in the same room, an extension alarm is available which can be placed outside and is audible for a considerable distance

The apparatus was made for me by Mr W L Eaton, 81, Daville Avenue, Virginia, Durban, Natal

Durban, Natal,
South Africa

W E B Edge
M B W'srand, M R C P, D C.H, D OBST

Reviews of Books

General Anæsthesia

Vol I *Basic Principles* Vol II *Techniques, Special Fields, and Hazards* Editors Frankis T Evans, M B, F F.A R C S, D A, anæsthetist, St Bartholomew's Hospital, St Mark's Hospital for Rectal Disease, and Royal Masonic Hospital, London, T Cecil Gray, M D, F F A R C S, D A, professor of anæsthesia, University of Liverpool London Butterworth 1959 Pp vol I 560, vol II 460 2 vols 147s

This is one of the best available books on general anæsthesia as a whole, aiming to provide postgraduates with a complete work of reference The first volume deals with the basic principles of anatomy, physiology, and pharmacology, and the second with anæsthetic techniques in general and, very adequately and clearly, with many special branches of anæsthesia There are some refreshingly brief and clear chapters on such hazards as explosions, other anæsthetic emergencies, and the anæsthetist's legal responsibilities

The editors chose to ask specialists in each field to write the various chapters, and this plan is not without its disadvantages in a book designed for young anæsthetists studying for higher examinations It is not easy for an anatomist to know precisely what anatomical knowledge is of most value to the anæsthetist, but it is surprising to find little reference to the anatomy of the veins and arteries of the arm in the chapter on anatomy

Writers who are specialists in a particular subject cannot always assess how much specialised knowledge in their subject may be taken for granted (for example, the section on pharmacology talks of an "enolic tautomer" without a word of explanation, and how many anæsthetists really know what a quaternary nitrogen atom is?) The physiologist who tells anæsthetists that "the administration of pure oxygen to deeply anæsthetised cyanosed patients is not without danger" must expect many of them to be perplexed The pharmacologist who talks of ether as a "chemically inert" substance will puzzle many who are looking for new non-inflammable anæsthetics for the very reason that ether can react with such chemical violence in the presence of a flame

In an otherwise beautifully clear chapter on the relaxants it is a pity that the drugs are not dealt with consistently For example, the pharmacology of *d*-tubocurarine is dealt with under the headings of Absorption, Excretion, Paralysant Activity, &c, but nothing is said of the absorption or excretion of gallamine If nothing is known, this could usefully be stated Several paragraphs are devoted to the M R.C blood bottles and giving-sets, but there is no mention of the now widely used disposable plastic sets The chapter on anæsthetic apparatus could well be expanded, or else omitted altogether As it stands, it is not sufficiently complete to meet the claims of the book But these minor criticisms of the first volume detract little from the value of the book as a whole Furthermore, the second volume has many chapters that are first-class examples of how a textbook should be written The chapter on the types of congenital heart-disease will be read with delight and relief by many anæsthetists whose minds are not clear on the subject. Similarly, controlled hypotension is dealt with fully and clearly, without unnecessary elaboration In the chapter on genitourinary anæsthesia, it is a joy to be reminded that simplicity is still compatible with good anæsthesia, and that momentary apnœa may be produced without the need for repeated intravenous injections

The book is not cheap, but it is outstandingly useful and well worth study by all who wish to keep up-to-date in anæsthesia

The Discovery of Reflexes

E G T Liddell, M D, F R S, Waynflete professor of physiology, University of Oxford London Oxford University Press 1960 Pp 174 30s

This book is Professor Liddell's tribute to Sherrington, his friend and master In the first four chapters he reviews the history of the physiology of the nervous system First he describes the structural basis of nervous function and the technical devices, especially the increasing refinements of the microscope, needed for morphological study this work culminated in the establishment of the neurone theory Then the problems of function and the early studies of electricity in living tissues are reviewed these findings prepared the way for an experimental approach to the nervous system The book then turns to the classical experiments which established the Bell-Magendie doctrine of specific nerve energies, and Marshall Hall and Muller's views on the nervous arc and the activity of the spinal cord the concept of reflex action was thus engendered In the final chapter, which is the heart of the book, Sherrington's own large and fructifying contributions to the study of nervous function are reviewed up to the time of his Silliman lectures, subsequently published as *The Integrative Action of the Nervous System*

Sherrington would have appreciated this book, for its balance, its lucidity, and especially its feeling for words In the earlier chapters the byways of scholarship are entertainingly explored in illustrating the main theme Old controversies and personalities are made to live again, but put in perspective by the author's dry comments How irritating the brash young du Bois-Reymond must have been—the more so, because he was nearly always right! How familiar the contretemps over priority between Bell and Magendie and others How pervasive the shadow of theological thought still was in the nineteenth century The final analysis and appreciation of Sherrington—both his main work and "his customary diversions on subjects which he noticed as he passed along on his crusade of inquiry"—is equally well done

This book can be recommended to the medical student as a pleasing introduction to the study of neurophysiology and to neurologists of all persuasions as a scholarly review of the historical background of this subject

The Physiological Basis of Diuretic Therapy

Robert F Pitts, PH D, M D, professor of physiology and biophysics, Cornell University Medical College, New York Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1960 Pp 332 78s

The practitioner who can find time to read and digest this book will, as the author says in an introduction, gain much intellectual satisfaction from rational therapy rationally applied It is one of the real pities of today that, despite our increasing understanding of health and disease, medicine is still so often empirical in its application, because the practitioner has so much to do and so little time for reading or thought This book is in two parts, and the first admirably summarises and discusses our knowledge of the interrelationships between the fluid compartments of the body and their ionic constitution and balance From this the book passes to a consideration of œdema formation, and the part played by the kidney in regulating water and salt balance The author has a long acquaintanceship with renal physiology, and the chapters in this section are excellent summaries of present knowledge Much of the information has not yet had time to reach the textbooks, and chapters IV, V, and VI might be recommended reading for medical students

The second part of the book builds on these foundations and considers the action and therapeutic use of diuretic agents, which are divided into two classes, physiological and pharmacological Each method of treatment and each drug are then considered in turn, with discussions of what they do and how, and in what conditions they may do good The book mentions doses, when substances should or should not be used, and how soon results may be expected, but it is not intended as a manual of treatment It is meant to, and does, supply general principles and much interesting detail At the end of each chapter there is a useful short list of references, and a summary which tempers the wind for weaker brothers The diuretics considered range from the old-established digitalis glycosides, xanthines, and mercurials of many kinds through cation-exchange resins and steroids to the latest sulfonamyl diuretics The last chapter deals briefly with some of the general complications of diuretic therapy Throughout, the author writes with clarity and authority, and this book is highly recommended

Diseases of the Skin

JAMES MARSHALL, M D, head of the department of dermatology, University of Stellenbosch Medical School Edinburgh E & S Livingstone 1960 Pp 944 84*s*

THE author clearly set out to write a book devoid of the pious nonsense which convinces the student that dermatology is bogus He has largely succeeded and it is safe to predict that his book will be popular it reads well, it is topical, comprehensive, factual, and on the whole well illustrated The author is a francophile and favours some unnecessarily odd nomenclature, always a bore to the student More seriously, he adopts the curiously obtuse attitude of the French towards the psychological features of dermatology, denial of which does not abolish In most other respects this is a good book

Surgeon Compassionate

FRIEDA SANDWITH London Peter Davies 1960 Pp 235 21*s*

THERE hangs, in the board-room of the Royal Free Hospital, a picture which shows a young man, elegantly dressed in the style of a hundred and thirty years ago, supporting a young woman who lies in rags on a doorstep The man is Dr William Marsden, and the incident depicted is his encounter in 1828 with a woman who was mortally ill, but who could not gain entrance to any hospital without a letter of introduction from its Governor It was that which prompted him to devote the rest of his life to the creation of a new hospital—one to which admission would be "free" in the most liberal sense of the word

Dr Marsden's great-granddaughter has now used the hospital minute-books and her family records to provide a very detailed and convincing account of his life Her story is enhanced by much unusual information about Marsden's background, and about such people as the "Toshers" and "pure-finders", who were numbered so largely amongst his patients ("Toshers" were sewer-hunters, who scavenged in the city drains, "Pure" was dog's dung which, being much in demand for tanning leather, was a very valuable commodity)

The early years of the Free Hospital were troubled by dissension amongst its governors, and by some very hostile Press reports On at least one occasion it incurred the wrath of Thomas Wakley, but it is pleasant to record that his son eventually became chairman of the hospital's committee of management, and that in 1867, when (after founding a second hospital) William Marsden died, *The Lancet* paid him unstinted praise as one who had done "signal service to mankind during his active and eventful life"

Henry E Sigerist on the Sociology of Medicine

Editor MILTON I ROEMER, M D, director of research, Sloan Institute of Hospital Administration, Cornell University New York M D Publications 1960 Pp 414 $6 75

Henry Sigerist, considered by many to be the greatest medical historian of our time, possibly of all time, was born in Paris in 1891 and was attracted to the study of languages By the time he was fifteen he was well versed in French, German English and Italian and was familiar with Greek, Latin, and Arabic Later he added Hebrew, Chinese, and Sanskrit Dissatisfied with the limits of philology he turned to science and finally to medicine becoming deeply interested in its history But his astute mind did not dwell only in the past He was a visionary of immense range, looking well and wisely into the future and always with the historical background in mind At the time of his death in 1957 he was engaged on an eight-volume history of medicine of which unhappily only the first two were completed He had intended to follow this with a four-volume *Sociology of Medicine*

The thirty-one essays in this book have been chosen from his abundant writings None are available elsewhere in book form They span a quarter of a century, from 1931 to 1955 Twenty-eight have been previously published but two are from manuscripts found among the Sigerist papers, and one is derived from an unpublished document submitted to the World Health Organisation They have been arranged mainly on geographical lines—Europe, America, other lands, special topics, and a group of general essays Much of the book is devoted to medical problems and trends in America

Current Unrest in the Medical World and the other three essays devoted to Europe explore European medical programmes and their endeavours to meet the needs of an urbanised society An Outline of the Development of the Hospital gives a short comprehensive history of the evolution of the modern hospital, and War and Medicine a dramatic account of the development of medicine in response to the demands of war The Place of the Physician in Modern Society is a sweeping analysis of the changing role of the physician in a changing society These are samples that show something of the scope of a book that is bound to interest medical and lay sociologists

A Symposium on pH and Blood Gas Measurement. (London J & A Churchill 1960 Pp 210 30*s*)—This volume reports one of the distinguished meetings arranged by the Ciba Foundation for a small group of participants, in this case apparently 25, though chapter V is credited to a contributor who is not listed as a participant The objects of the gathering were "to exchange ideas on means of measurement, to discuss their clinical significance, and to consider how the abnormalities detected could be expressed most clearly to the clinician" In the book itself, the emphasis is very heavily on the first of these, and this is not at all a bad thing, for the analytical difficulties have been a major deterrent to the permeation of acid-base "know-how" into clinical medicine. The participants included scientific staff from the manufacturers of pH-meters, and ten of the 12 chapters are concerned with analytical methods Of these surveys, that by P Astrup, on ultra-micro-methods for determining pH, pCO_2, and standard bicarbonate in capillary blood, is outstanding, while J W Severinghaus looks perhaps more to the future in his account of electrodes capable of monitoring blood O_2 and CO_2 These analytical chapters are important not only for clinical chemists but also for anaesthetists and the operators of artificial hearts and respirators While welcoming the implied tribute to a great clinical chemist, we note with mixed feelings the appearance of a new verb "to Van Slyke" with apparently a present participle "Van Slyking" The second objective, the discussion of clinical significance, crops up occasionally in discussion, and is the subject of a good short chapter by V Wynn, and the third objective, making the clinician understand, receives only passing comment in the general discussion. The title in fact describes the contents more accurately than does the foreword, and within these limits this is an excellent book It was edited by Prof R F Woolmer, with the aid of Miss Joy Parkinson.

Recent Research in Freezing and Drying (Oxford Blackwell Scientific Publications 1960 Pp 320 63*s*)—Living cells sometimes survive freezing and drying how they may tolerate these extremes of physical environment has in recent years become a subject for detailed study In this new book the editors, Dr A S Parkes and Dr Audrey Smith, themselves pioneers in this work, have collected a series of authoritative contributions based on papers given in London in 1958 by workers from many countries The articles mainly concern the biophysics of these processes and their application to microbiology and to surgery They can be thoroughly recommended

THE LANCET

LONDON 18 JUNE 1960

Leptospirosis

KNOWLEDGE of the diseases caused in man and animals by leptospires has greatly increased in the past ten years The scientific foundation was the isolation in Weil's disease of *Leptospira icterohaemorrhagiæ*, by Japanese[1] and German[2,3] workers in 1914 and 1915 Since then over forty types of leptospires have been distinguished by serological tests and have been found unevenly distributed over most of the temperate and subtropical countries of the world In Nature these are parasitic on a very wide range of rodents, causing disease in them only occasionally Leptospires are excreted in large numbers in the urine of infected rodents Domestic animals—including dogs, pigs, cattle, sheep, goats, and horses—acquire leptospires from rodents or from one another and are much more prone than rodents to acute or chronic disease as well as to a carrier state with urinary excretion Man becomes infected mostly from rodents but sometimes from domestic animals, transmission of infection from man to man has been very rare In Great Britain infections in man have so far been found due only to *L icterohæmorrhagiæ* from rats or *L canicola* from dogs, and until recently these two types of leptospires were the only ones discovered in this country In 1958, however, BROOM and COGHLAN[4] reported finding *L ballum* in wood-mice and voles and leptospires related to *L sejroe* and *L saxkoebing* in voles in Scotland An article in this issue on p 1326 describes an investigation by the late DR BROOM and by DR COGHLAN of a leptospire from a hedgehog caught near Edinburgh This strain is related to *L australis A* and *L muenchen* There may thus be unrealised sources of leptospirosis in this country

In most countries of Europe, Asia, North and South America, and Australasia infections of man and domestic animals are commoner than in Great Britain, and they have been found due to several types of leptospires from a great variety of rodents, the concentration of the disease is greatest in Indonesia and Malaya, where about thirty infective types have been found The occasions of infection everywhere are predominantly agriculture—especially harvesting cereals, sugar, rice, or vegetables—and the care of domestic animals on farms or at home Nearly related circumstances arise in handling and preparing meat Other occasions are mining, sewer and canal work, and bathing in fresh water Man is infected usually by contact of skin, conjunctiva, or mucous membranes with leptospires from animals' urine, and less commonly by contact with infected animal tissues or bites by rodents or dogs The disturbance ranges from severe hepatitis with jaundice, severe nephritis, meningitis, and general toxæmia to a mild febrile illness with or without obvious meningitis Any of the types of leptospire may cause the milder disease, but the severe, possibly fatal, form is almost confined to infection by those types which commonly cause jaundice Of these, *L icterohæmorrhagiæ* is the most outstanding, but others, such as *L andaman A*, *L australis A*, *L bataviæ*, and *L pyrogenes* have caused severe and fatal infection.

After 1915 the subject was perhaps most intensively studied in Japan, the Netherlands and Indonesia, Andaman Islands, Malaya, Switzerland, Denmark, Germany, Russia, Italy, Australia, South America, France, and Great Britain In the past decade much work has been done in Malaya, New Zealand, Israel, and the U S A (Of the several monographs recording progress,[5–9] that by ALSTON and BROOM[9] is perhaps the most valuable) In Malaya the infection was common among British and Asian soldiers in the guerilla warfare MCCRUMB et al[10] showed that leptospirosis accounted for 35% of all acute febrile illnesses among military personnel, and for 13% of the illnesses in 238 adult male Asian civilians investigated for the cause of pyrexia of unknown origin TURNER et al[11] have lately reviewed infections in Malaya, and in a further series found definite or suggestive serological evidence of leptospirosis in about 21% of 130 cases of undiagnosed pyrexia EDWARDS and DOMM[12] name twelve types of leptospires causing disease in the U S A The human disease was found to be associated with farming, veterinary and food-handling occupations, service in the Armed Forces, and bathing In animals it produced abortion and loss of condition of cattle, pigs and sheep These workers believe that meningitis will be found in 80-90% of all cases of leptospirosis if the cerebrospinal fluid is examined in the second week, the patient recovers completely regardless of management, and they agree with GSELL[7] that this meningitis reflects an antigen-antibody reaction

With the growing recognition of this disease there has been much experimental investigation of the organisms and their effects on the animals which they invade Electron micrographs[9] by J D FULTON and D F SPOONER have suggested fine details of cross-striation on the axial filament which twines round the main body of a leptospire, and this formation may be the site of the mechanism of motility The types of leptospires—like most of the types of salmonella—show only small metabolic differences compared with their variety of antigens. Some leptospires have been analysed by SCHNEIDER[13,14], ROTHSTEIN, and HIATT[15] concluded from ethanol extraction and dialysis that there were peripheral somatic antigens. The pathogenic mechanism of leptospires is far from fully understood, but FAINE[16] has suggested from culture of virulent and avirulent strains in different media and at different temperatures that the relative resistance of virulent leptospires to conditions resembling those in vivo may explain their survival in infected animals.

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[2] Hübener E A., Reiter, H *Dtsch med Wschr* 1915, 41, 1275, *ibid* 1916, 42, 131

[3] Uhlenhuth, P , Fromme, W *Med Klin* 1915, 11, 1202

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[5] Walch-Sorgdrager, B *Bull Hlth Org L o N* 1939, 8, 143

[6] Rimpau W Die Leptospirose Munich, 1950

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In severe infections the critical lesion is almost always an acute lower-nephron nephrosis similar to that sometimes found in crush injuries, burns, or incompatible blood-transfusions. These lesions may be due to vasoconstriction, but the mechanism is still uncertain. Oliguria and anuria with rise of blood-urea indicate their severity, and are a guide to the essential treatment, which is by the conservative régime of BULL[17] and, if necessary, the "artificial kidney". Leptospirosis leaves very little damage in the kidneys, liver, or meninges in patients who recover (in dogs chronic and slowly fatal nephritis commonly develops). In contrast with the treatment of nephritis, antibiotic treatment of the disease is less important. All types of leptospire are sensitive to many antibiotic drugs, including penicillin, streptomycin, and the tetracyclines, but to be effective in experimental infection such treatment had to be started during the incubation period.[18] BROOM[19] showed that penicillin had not reduced the death-rate from Weil's disease in Great Britain up to 1950. The evidence on the value of antibiotics in the milder forms of disease is at present conflicting. In Malaya, FAIRBURN and SEMPLE[20] found that chloramphenicol or penicillin provided no benefit, but soon afterwards MACKAY-DICK and ROBINSON[21] concluded that administration of penicillin begun in the first few days of illness hastened recovery.

In prevention, vaccination has been considered successful in the Italian rice fields,[22] where those at risk are concentrated at the work, but differences of types and more variable exposure have operated against its effectiveness elsewhere. In sugar-cane fields, rice fields, farms, slaughterhouses, fish-gutting sheds, food stores, refuse dumps, sewers, and canals rodents have been destroyed or their access prevented, and leptospires excreted in their urine or in that of domestic animals have been killed by burning or by chemicals. The use of waterproof boots and other protective clothing in piggeries and sewers, and where possible provision of hot water and soap for hand-washing and antiseptic first-aid treatment for cuts and abrasions, have been successful. Prophylactic administration of penicillin after injury has been advocated, but this method failed in a carefully observed case of laboratory infection[23] in which 6 million units of penicillin was given orally during three days, starting one hour after infection.

Myocardial Injury from Therapeutic X Rays

WHEN the myocardium is included within therapeutic X-ray fields, electrocardiographic changes may result. The myocardium may be thus implicated during therapeutic X-radiation of breast cancer and of intrathoracic lesions, such as bronchogenic carcinoma, malignant mediastinal masses, and tumours of the thymus. Critical studies of such cases are complicated by the effects on cardiac function (such as dysrhythmias, or displacement, or mediastino-pericarditis) which these lesions may, of themselves, produce. For critical analysis the best material is provided by cases of breast carcinoma in which X-radiation has been applied: JONES and WEDGWOOD[24] report on 25 such cases and CATTERALL and EVANS[25,26] on 20. The patients were all examined clinically, radiologically, and electrocardiographically before radiotherapy, and at intervals afterwards. No clinical or radiological abnormalities attributable to X-ray therapy were noted in either series, so the discussion centres on the interpretation of electrocardiographic changes.

Of JONES and WEDGWOOD's 25 patients, 21 had electrocardiographic (E.C.G.) changes after radiotherapy, but these workers regarded such changes as pathological in only 4. The particular difficulty is to interpret T-wave changes confined to leads V_1 and V_2—leads which overlie the portion of the heart most exposed to radiation when parasternal fields are used. WHITFIELD and KUNKLER[27] attributed changes in these leads to direct damage to the heart-muscle itself, for the E.C.G. changes corresponded in time with the erythematous skin reactions. JONES and WEDGWOOD regarded the E.C.G. changes in 17 of their 21 patients as non-pathological and due to various causes such as physiological variations in E.C.G. tracings in the same individual, the effects of posture and respiratory movement, and the influence of the operation scar, of skin reactions to X rays, and of breast size. Changes they accepted as pathological consisted in flattening and inversion of T waves in leads V_4 to V_7, which overlie the left ventricle (2 cases), and ST-segment changes (2 cases). These changes are non-specific, and JONES and WEDGWOOD suggest that small areas of pericarditis would account for them. They believe that pre-existing ischæmic heart-disease may have been a factor in all 4 cases, and that the E.C.G. changes, while pathological, were trivial, unaccompanied by symptoms, and usually transient, and "should not be used on present evidence to limit essential radiotherapy".

CATTERALL's patients were treated by glancing fields of X rays, not by direct parasternal fields, and a method was devised to ascertain the part of the heart actually irradiated and the dose received. By this technique of

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21 Mackay-Dick, J., Robinson, J. F. *ibid.* 1959, i, 100.
22 Babudieri, B. *Zbl. Bakt.* 1957, 168, 260.
23 Broom, J. C., Norris, T. S. M. *Lancet*, 1957, i, 721.
24 Jones, A., Wedgwood, J. *Brit. J. Radiol.* 1960, 33, 139.
25 Catterall, M. *ibid.* p. 159.
26 Catterall, M., Evans, W. *Brit. Heart J.* 1960, 22, 168.
27 Whitfield, A. G. W., Kunkler, P. B. *ibid.* 1957, 19, 53.

irradiation, E.C.G. changes were observed only in patients who had the left side of the chest irradiated. Of the 12 such cases, significant E.C.G. changes were found in 9; in the remaining 3 cases marker films had already shown that the myocardium would receive less than 1000r. T-wave changes developed in the 9 patients; these were noted four months after irradiation, persisted at nine months, but had disappeared at twelve months. The changes were attributed to temporary myocardial damage.

Catterall made anatomical dissections which show so close a relation between the internal mammary lymph-nodes and the heart that it is difficult to believe that a significant dose of X rays can be given to the former without injuring the latter. Experimental work[28–30] has shown that X-radiation may cause direct injury to the myocardium (evident macroscopically, histologically, and in the electrocardiogram) within days or a few weeks after irradiation. What may be more important is the endarteritis and subsequent vascular occlusion caused by X rays, contributing to the post-radiation syndromes which arise after several months—a latent period evident in radiation nephritis[31 32] and in radiation myelitis.[33–36] Radiation arteritis of the coronary vessels is a distinct possibility. **Pearson**,[37] for instance, described extensive myocardial infarction six months after chest irradiation in 2 women under the age of 50, observing that "the attacks were of great severity, accompanied by disturbances of conduction and followed by a degree of clinical and electrocardiographic recovery that one could not expect after atheromatous occlusion."

Two main factors have prevented proper appreciation of the incidental dangers of X-ray therapy—the long latent period between the therapy and important clinical manifestations of such incidental damage, and the understandable concentration of the radiotherapist on the tumour. It has been known for about thirty years that irradiation may damage the heart, but apparently so far no systematic long-term clinical observations on large numbers of patients irradiated in this way have been made. The reports discussed here are useful—though **Jones** and **Wedgwood** possibly underestimate the problem—but their value is limited by the smallness of the series, bearing in mind that sensitivity to X rays notoriously varies between different people. We agree that the risk of damage to structures other than the malignant tumour may have to be accepted when radiotherapy is the best line of treatment. We must know, however, what such incidental risks amount to. Enthusiasm for, and skill in, a technique of therapy should be associated with unbiased evaluation of the total risks to the patient.

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[29] Warthin, A. S., Pohle, E. A. *Arch. intern. Med.* 1929, 43, 15.
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Annotations

GENIUS AND CULTURAL PROGRESS

Students of society, present and past, have often asked themselves what are the agents that determine the rapid, almost miraculous, advance shown by certain cultures at different times. Offering some views on this crucial topic in his Hobhouse lecture at University College on May 30, Sir Aubrey Lewis, professor of psychiatry in the University of London, pointed to the inherent stability and conservatism of societies, which, he said, incorporated ideas of radical change only under conditions of dire threat. "Progress" he thought was hard to assess, for while, in general, material, æsthetic, and social values ran parallel, this was not always so: for example, present material achievements were enormous, but they had scarcely been equalled in the æsthetic and moral spheres. Environmental pressures—from climate, contact with other societies, and so on—were undeniable, but their extreme forms (e.g., upon the Eskimos) were uncommon and could not account for the most dramatic advances. Though, historically, some logical order could be seen—for instance, in scientific discovery—it was impossible to tell why a certain triumph was achieved by a given man at a given time. The sociologist Robert Merton, in his careful study, had attributed the 17th-century rise of science to the "Calvinist spirit" of the puritans—a spiritually derived flow of practical activity, by those believing themselves specially chosen of God, which later became secularised (some discoveries actually antagonising the theologians). But different cultures undoubtedly provided different circumstances for such flowering. Bitter denial of legitimate progress, such as we still see in the field of art, was no longer a danger in science, and over-credulity, if anything, was more probable. Scepticism Sir Aubrey did not regard as a harmful commodity; indeed if it had been more in evidence latterly humanity would have been saved enormous suffering. Minds, it had been said, tended to fall into a critical-destructive or creative-accepting group; the merits and demerits of these antitheses were not easy to judge.

The concept of the "great man" in this context had been disparaged but it undoubtedly contained much truth. Such exceptional individuals—e.g., in science—were usually outstanding personalities in their own right, the apex being reached, Sir Aubrey thought, by men like Darwin, Galileo, and Newton. Great men were, in large measure, obviously products of their society. Much dispute had surrounded the alleged characteristics of such people, and criticism of them often arose from the injured narcissism of lesser mortals, who raised their own self-esteem by pulling the mighty from their pedestals: such could not fail to impede advance. Genius had been described as "a transcendent capacity for taking trouble", but there was much to be said for Samuel Butler's suggestion that it was an infinite capacity for getting into trouble! In particular, Sir Aubrey differed from the views of Kretschmer and others equating genius with insanity: the idea that a psychopathic element was essential he believed to be erroneous, though comforting to some. Genius and mental disease might coexist, though probably no more commonly than might be randomly expected, and the affliction was often limited to old age. Early schizophrenia, mania, or toxic psychoses might provide the exceptional mind with flashes of intuition and release of inhibition, though essentially the schizoonly small metabolic differences compared with their variety of antigens Some leptospires have been analysed by Schneider[13][14], Rothstein, and Hiatt[15] concluded from ethanol extraction and dialysis that there were peripheral somatic antigens The pathogenic mechanism of leptospires is far from fully understood, but Faine[16] has suggested from culture of virulent and avirulent strains in different media and at different temperatures that the relative resistance of virulent leptospires to conditions resembling those in vivo may explain their survival in infected animals

In severe infections the critical lesion is almost always an acute lower-nephron nephrosis similar to that sometimes found in crush injuries, burns, or incompatible blood-transfusions These lesions may be due to vasoconstriction, but the mechanism is still uncertain Oliguria and anuria with rise of blood-urea indicate their severity, and are a guide to the essential treatment, which is by the conservative régime of Bull[17] and, if necessary, the " artificial kidney " Leptospirosis leaves very little damage in the kidneys, liver, or meninges in patients who recover (in dogs chronic and slowly fatal nephritis commonly develops) In contrast with the treatment of nephritis, antibiotic treatment of the disease is less important All types of leptospire are sensitive to many antibiotic drugs, including penicillin, streptomycin, and the tetracyclines, but to be effective in experimental infection such treatment had to be started during the incubation period[18] Broom[19] showed that penicillin had not reduced the death-rate from Weil's disease in Great Britain up to 1950 The evidence on the value of antibiotics in the milder forms of disease is at present conflicting In Malaya, Fairburn and Semple[20] found that chloramphenicol or penicillin provided no benefit, but soon afterwards Mackay-Dick and Robinson[21] concluded that administration of penicillin begun in the first few days of illness hastened recovery

In prevention, vaccination has been considered successful in the Italian rice fields,[22] where those at risk are concentrated at the work, but differences of types and more variable exposure have operated against its effectiveness elsewhere In sugar-cane fields, rice fields, farms, slaughterhouses, fish-gutting sheds, food stores, refuse dumps, sewers, and canals rodents have been destroyed or their access prevented, and leptospires excreted in their urine or in that of domestic animals have been killed by burning or by chemicals The use of waterproof boots and other protective clothing in piggeries and sewers, and where possible provision of hot water and soap for hand-washing and antiseptic first-aid treatment for cuts and abrasions, have been successful Prophylactic administration of penicillin after injury has been advocated, but this method failed in a carefully observed case of laboratory infection[23] in which 6 million units of penicillin was given orally during three days, starting one hour after infection

Myocardial Injury from Therapeutic X Rays

When the myocardium is included within therapeutic X-ray fields, electrocardiographic changes may result The myocardium may be thus implicated during therapeutic X-radiation of breast cancer and of intrathoracic lesions, such as bronchogenic carcinoma, malignant mediastinal masses, and tumours of the thymus Critical studies of such cases are complicated by the effects on cardiac function (such as dysrhythmias, or displacement, or mediastino-pericarditis) which these lesions may, of themselves, produce For critical analysis the best material is provided by cases of breast carcinoma in which X-radiation has been applied Jones and Wedgwood[24] report on 25 such cases and Catterall and Evans[25][26] on 20 The patients were all examined clinically, radiologically, and electrocardiographically before radiotherapy, and at intervals afterwards No clinical or radiological abnormalities attributable to X-ray therapy were noted in either series, so the discussion centres on the interpretation of electrocardiographic changes

Of Jones and Wedgwood's 25 patients, 21 had electrocardiographic (E C G) changes after radiotherapy, but these workers regarded such changes as pathological in only 4 The particular difficulty is to interpret T-wave changes confined to leads V_1 and V_2—leads which overlie the portion of the heart most exposed to radiation when parasternal fields are used Whitfield and Kunkler[27] attributed changes in these leads to direct damage to the heart-muscle itself, for the E C G changes corresponded in time with the erythematous skin reactions Jones and Wedgwood regarded the E C G changes in 17 of their 21 patients as non-pathological and due to various causes such as physiological variations in E C G tracings in the same individual, the effects of posture and respiratory movement, and the influence of the operation scar, of skin reactions to X rays, and of breast size Changes they accepted as pathological consisted in flattening and inversion of T waves in leads V_4 to V_7, which overlie the left ventricle (2 cases), and ST-segment changes (2 cases) These changes are non-specific, and Jones and Wedgwood suggest that small areas of pericarditis would account for them They believe that pre-existing ischæmic heart-disease may have been a factor in all 4 cases, and that the E C G changes, while pathological, were trivial, unaccompanied by symptoms, and usually transient, and " should not be used on present evidence to limit essential radiotherapy "

Catterall's patients were treated by glancing fields of X rays, not by direct parasternal fields, and a method was devised to ascertain the part of the heart actually irradiated and the dose received By this technique of

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13 Schneider, M D *Exp Parasit* 1955, 4, 107
14 Schneider, M D , McLaughlin, J , Jr *J Bact* 1955, 70, 87
15 Rothstein, N , Hiatt, C W *J Immunol* 1956, 77, 257
16 Faine, S *J Bact* 1959, 77, 599
17 Bull, G M *Lancet*, 1955, i, 731, 777
18 Alston, J M , Broom, J C *Brit med J* 1944, ii, 718
19 Broom, J C *ibid* 1951, ii, 689
20 Fairburn, A C , Semple, S J G *Lancet*, 1956, i, 13
21 Mackay-Dick, J , Robinson, J F *ibid* 1959, i, 100
22 Babudieri, B *Zbl Bakt* 1957, 168, 280

23 Broom, J C , Norris, T St M *Lancet*, 1957, i, 721
24 Jones, A , Wedgwood, J *Brit J Radiol* 1960, 33, 138
25 Catterall, M *ibid* p 159
26 Catterall, M , Evans, W *Brit Heart J* 1960 22 168
27 Whitfield, A G W , Kunkler, P B *ibid* 1957, 19, 53

irradiation, E C G changes were observed only in patients who had the left side of the chest irradiated. Of the 12 such cases, significant E C.G changes were found in 9, in the remaining 3 cases marker films had already shown that the myocardium would receive less than 1000r T-wave changes developed in the 9 patients, these were noted four months after irradiation, persisted at nine months, but had disappeared at twelve months. The changes were attributed to temporary myocardial damage.

CATTERALL made anatomical dissections which show so close a relation between the internal mammary lymph-nodes and the heart that it is difficult to believe that a significant dose of X rays can be given to the former without injuring the latter. Experimental work[28-30] has shown that X-radiation may cause direct injury to the myocardium (evident macroscopically, histologically, and in the electrocardiogram) within days or a few weeks after irradiation. What may be more important is the endarteritis and subsequent vascular occlusion caused by X rays, contributing to the post-radiation syndromes which arise after several months—a latent period evident in radiation nephritis[31 32] and in radiation myelitis[33-36]. Radiation arteritis of the coronary vessels is a distinct possibility. PEARSON,[37] for instance, described extensive myocardial infarction six months after chest irradiation in 2 women under the age of 50, observing that "the attacks were of great severity, accompanied by disturbances of conduction and followed by a degree of clinical and electrocardiographic recovery that one could not expect after atheromatous occlusion"

Two main factors have prevented proper appreciation of the incidental dangers of X-ray therapy—the long latent period between the therapy and important clinical manifestations of such incidental damage, and the understandable concentration of the radiotherapist on the tumour. It has been known for about thirty years that irradiation may damage the heart, but apparently so far no systematic long-term clinical observations on large numbers of patients irradiated in this way have been made. The reports discussed here are useful—though JONES and WEDGWOOD possibly underestimate the problem—but their value is limited by the smallness of the series, bearing in mind that sensitivity to X rays notoriously varies between different people. We agree that the risk of damage to structures other than the malignant tumour may have to be accepted when radiotherapy is the best line of treatment. We must know, however, what such incidental risks amount to. Enthusiasm for, and skill in, a technique of therapy should be associated with unbiased evaluation of the total risks to the patient.

Annotations

GENIUS AND CULTURAL PROGRESS

STUDENTS of society, present and past, have often asked themselves what are the agents that determine the rapid, almost miraculous, advance shown by certain cultures at different times. Offering some views on this crucial topic in his Hobhouse lecture at University College on May 30, Sir Aubrey Lewis, professor of psychiatry in the University of London, pointed to the inherent stability and conservatism of societies, which, he said, incorporated ideas of radical change only under conditions of dire threat. "Progress" he thought was hard to assess, for while, in general, material, æsthetic, and social values ran parallel, this was not always so; for example, present material achievements were enormous, but they had scarcely been equalled in the æsthetic and moral spheres. Environmental pressures—from climate, contact with other societies, and so on—were undeniable, but their extreme forms (e g, upon the Eskimos) were uncommon and could not account for the most dramatic advances. Though, historically, some logical order could be seen—for instance, in scientific discovery—it was impossible to tell why a certain triumph was achieved by a given man at a given time. The sociologist Robert Merton, in his careful study, had attributed the 17th-century rise of science to the "Calvinist spirit" of the puritans—a spiritually derived flow of practical activity, by those believing themselves specially chosen of God, which later became secularised (some discoveries actually antagonising the theologians). But different cultures undoubtedly provided different circumstances for such flowering. Bitter denial of legitimate progress, such as we still see in the field of art, was no longer a danger in science, and over-credulity if anything, was more probable. Scepticism Sir Aubrey did not regard as a harmful commodity, indeed if it had been more in evidence latterly humanity would have been saved enormous suffering. Minds, it had been said, tended to fall into a critical-destructive or creative-accepting group, the merits and demerits of these antitheses were not easy to judge.

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28 Hartman, F W, Bollinger, A, Doub, H F, Smith, F J *Bull Johns Hopk Hosp* 1927, 41, 36
29 Warthin, A S, Pohle, E. A *Arch intern Med* 1929, 43, 15
30 Hartman F W *ibid* p 32.
31 Luxton, R. W *Quart J Med* 1953, 22, 215
32 Wilson, C., Ledingham, J M, Cohen, M *Lancet*, 1958, i, 9
33 Boden, G *Brit J Radiol* 1948, 21, 464
34 Boden, G *J Fac Radiol, Lond* 1950, 2, 80
35 Russell, D S, Wilson C W, Tansley, K. *J Neurol Neurosurg Psychiat* 1949, 12, 187
36 Dynes, J B, Smedal, M. I *Amer J Roentgenol* 1960, 83, 78
37 Pearson, H E S *Lancet*, 1958, i, 222

phrenic process caused impoverishment and decay. Depression—" the dark night of the soul "—could add artistic depth, but the disturbed mind could not meet the demands of science, nor could mental illness beget great works and bring them to fruition. Intelligence played an important part, but beyond a certain level less quantifiable personality factors were crucial elements in success—stability, satisfactory marriage, and so forth—and with personality distortions a high intelligence quotient was, indeed, dangerous. But, geniuses apart, all scientific achievement depended on careful dedicated research by numbers of more " ordinary " people.

In conclusion, Sir Aubrey criticised our current preoccupation with abnormal and subnormal aspects of personality and suggested that psychologists, sociologists, and psychoanalysts should look more at the positive features of human beings, and at the possible ways these attributes may be nurtured. The potential powers of the human mind, as shown particularly in infant prodigies, were almost inconceivably vast, and such study might help to guide and hasten cultural advance.

UNIVERSITY PLAN FOR NEWCASTLE

A SPECIAL convocation of the University of Durham will next week consider the separation of the Durham and Newcastle divisions of the university and the establishment of an independent university in Newcastle. This step has the support of the governing bodies of both divisions.

The University of Durham was founded in 1832. Two years later, and quite independently, the " Newcastle upon Tyne School of Medicine and Surgery " was established. In 1852 the school became associated with the university, and from 1870 it was known as the " University of Durham College of Medicine ". In 1871 the " University of Durham College of Physical Science " opened in Newcastle—its name being changed to Armstrong College in 1904. Finally, the College of Medicine and Armstrong College were united in 1937 as King's College, which constitutes the Newcastle division of the University of Durham.

With the growth and development of both divisions the question of separation has long been under discussion. About ten years ago a proposal to change the name of the University to " University of Durham and Newcastle " was defeated by graduates in convocation—probably wisely, since it would have done little to solve the problems inherent in running a federal university whose divisions are fifteen miles apart. The difficulties are by no means only administrative but involve the academic control of curricula and examinations. Now Durham has 1600 students and Newcastle 3600, and they have been asked to prepare respectively for 3000 and 6000 by 1970.

Several, but not all, of the major faculties are now represented in each division. Medicine, as well as some others, is pursued only in Newcastle. Here also is a large dental school. Separation, if it comes, will be regretted by a large number of graduates, especially in medicine. Probably the great majority of these cherish the association of their school with the ancient city and cathedral of Durham, and they believe also that the prestige of Durham medical degrees is something not readily replaced. Full appreciation of the wider issues involved may not be easy. We can safely say, however, that those who regret the prospect of separation, and many who approve it, would be even more disturbed if the new university were given any other name than that of the city of Newcastle in which it has grown from small beginnings to one of the largest provincial university institutions.

CONTINUING SECULAR TREND IN GROWTH

IT is now well established that there has been a continuous trend toward earlier maturation in children in Western Europe and America during the past hundred years: the age of menarche has been getting earlier by approximately 4 months per decade, at least during the present century.[1] This trend shows no signs as yet of abating. The two latest items of information are from schools in Sussex and from the London County Council. In 1950 Wilson and Sutherland[2] reported a mean age of menarche of 13.38 years for a sample of children attending Dorset day-schools, and now, nearly ten years later, they report a figure of 13.03 years for children attending Sussex day-schools.[3] Since the circumstances of these two samples are believed not to differ it seems that the difference between these figures is attributable to the secular trend, which works out at very close to the figure of 4 months per decade. The recent survey carried out by the London County Council will, we understand, show a very similar trend in comparison with the figures of 5 years ago. The average age of menarche in this country, at least in the south, is evidently now just about 13.0 years. Clearly the trend may be expected to stop soon, but there is still no evidence of its doing so. The importance of future periodic surveys should be obvious both to medical and to educational authorities.

A FRUITFUL CENTURY

THE National Hospital for the Paralysed and Epileptic received its first patients, at 24, Queen Square, Bloomsbury, in June, 1860, and next week it will celebrate its centenary.

It was founded through the efforts of Miss Johanna Chandler, aided by her sister Louisa, and the good will of Alderman David Wire, lord mayor of London in 1859, and himself a sufferer from a chronic nervous disease. At a Mansion House dinner in November, 1859, a society was formed for the purpose of establishing and maintaining a hospital, and a board of management was set up with David Wire as chairman. Two physicians were later appointed in preparation for the opening—J. S. Ramskill, assistant physician to the London Hospital, and C. E. Brown-Séquard, who, with an international reputation already established, had now decided to set up in practice in London. The hospital rapidly became popular, and another physician and surgeon were appointed in 1860. In 1862 a young man named Hughlings Jackson, destined to become the greatest figure in British neurology, was appointed assistant physician, with the additional duty of visiting patients in their homes. When Brown-Séquard resigned on leaving London in 1863, another physician was appointed, Jackson being passed over at that time. In the next ten years, those joining the staff included a group from University College Hospital—Russell Reynolds, H. C. Bastian, and William Gowers—all three of whom, as well as Jackson, later became fellows of the Royal Society. Within a few years the hospital had acquired the adjoining

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1. Tanner, J. M. Growth at Adolescence. Oxford, 1955.
2. Wilson, D. C., Sutherland, I. *Brit. med. J.* 1950, ii, 862.
3. Wilson, D. C., Sutherland, I. *J. Obstet. Gynæc. Brit. Emp.* 1960, 67, 320.

houses, and it has gradually extended until now it occupies more than half the east side of Queen Square, with activities overflowing into adjacent buildings.

From the beginning, the hospital had a high academic standing, and Brown-Sequard's weekly lectures were the start of the present Institute of Neurology. Although some outstanding experimentalists, such as Brown-Sequard, David Ferrier, and Victor Horsley, were members of its honorary staff, the fame of the National Hospital, like that of Charcot and his school in France, was founded on clinical neurology. Ferrier's experimental observations on the localisation of function in the brain were the complement of the clinicopathological observations of Jackson, which were based particularly on the study of partial convulsions and those beginning unilaterally. Jackson's chief legacy, however, is not clinical observations but a philosophy of neurology; he was always looking for the general laws behind the individual phenomena. "In this regard," as Sir Gordon Holmes has said, "his hypotheses of evolution and dissolution of function and of release of function, his conception of the unit of referential speech as the proposition and not simply the word, stand out as amongst his greatest contributions." Clinical study led to the differentiation of diseases and syndromes, and these were magnificently described in William Gowers' *Manual of Diseases of the Nervous System*. This was based on his own observations, and his descriptions of disease were masterly.

To the next generation of Queen Square physicians belong the classical description of subacute combined degeneration of the cord by Risien Russell, F. E. Batten, and James Collier (following earlier observations by James Taylor), Holmes'—also classical—work on the symptoms of cerebellar disorders and on the cortical representation of vision, and Kinnier Wilson's account of progressive lenticular degeneration. J. G. Greenfield, as the first whole-time pathologist, reaped a rich harvest, and has a number of first descriptions to his credit. In 1893, Gowers had written that "idiopathic cerebritis" was almost unknown, and this state of affairs persisted till the epidemic of encephalitis lethargica during and after 1919. Greenfield studied its pathology with Farquhar Buzzard, and then investigations of other forms of encephalitis came thick and fast—those following vaccination and measles, other forms of demyelinating encephalitis, the encephalitis periaxialis of Schilder (whose clinical recognition is due to Collier) and its different types, and then the leucoencephalitis of children and the varieties of inclusion-body encephalitis. In fact except for cerebral abscess and syphilis, our knowledge of inflammation of the brain has all been gained within a generation.

Outpatient teaching was developed at an early stage, particularly by Gowers, but nowadays teaching occupies a far bigger place than ever before. The former medical school has become the Institute of Neurology, part of the University of London. Also the hospital houses two research units set up by the Medical Research Council. But though "The National" has in this way gone far beyond the purposes of its founders, it preserves, explicitly as well as implicitly, part of its original charitable foundation. When the hospital was taken over by the National Health Service, the society which formerly ran it remained in being. In 1902 it had received a royal charter, and as the "Chartered Society" it not only acts as the "friends of the hospital" but also carries on the second of the forms of social service established by Johanna Chandler—namely, a pension fund for paralysed patients. The number of pensions is now about a hundred, and though they are small they help to meet the special needs of paralysed patients. Sir Ernest Gowers has been chairman of this society for many years.

BACKED BY THE COMMUNITY

LIKE many other admirable institutions which have been started by private good will, our system of university awards and scholarships has been taken over and developed by the community as a form of enlightened self-interest. A modern State which needs a great many highly educated citizens must ensure that enough suitable young people have an opportunity to attend a university. Already over 80% of our students hold awards from public funds. In 1951–52 the cost of these university awards was £5·6 million, in 1958–59 it was £21·6 million. The need for graduates continues to grow steadily, and two years ago the Minister of Education and the Secretary of State for Scotland appointed a committee, under the chairmanship of Sir Colin Anderson, to consider the present system of university grants. The committee, which has now reported,[1] besides suggesting many useful modifications of detail, have recommended two major changes.

The first, which has the support of the whole committee, is that any student (ordinarily resident in Great Britain) who is accepted by a university and who has attained a minimum entry qualification (2 G.C.E. passes at A level in England and Wales) should automatically qualify for an award. This would in effect shift the responsibility for selection from the local authorities to the universities, abolish one academic hurdle, and offer equal facilities to students from every part of the country. Public funds cannot be used to finance the "perpetual student", and awards would ordinarily be given only for first degree courses. But the committee recommend that the claims of students who for some good reason wish to take a further course should be considered sympathetically. As a deserving exception of this kind they specially mention "exceptionally able medical students who are recommended to interrupt their medical courses in order to undertake a specialist course in a related scientific subject, such as bio-chemistry."

The second important change which the report discusses is the controversial issue of parental contributions to awards. Here the committee were themselves divided. Eleven members recommended that parental contributions should be abolished, five members would like to see them retained at any rate for the present, though in a modified form. All were agreed that some young people lose the chance of a university education because the present system falls hardly on their parents. The "abolitionists" in presenting their case make the further point that by the new "family pattern" many young people who take jobs became financially independent of their parents in their teens. Should not the student, who must work at least as hard as his wage-earning contemporaries, also be given a measure of independence? The committee also draw attention to the growing number of scholarships offered without regard to parental income by industrial bodies and nationalised boards and ask whether these may not deflect an undue proportion of students into certain careers, leaving others, such as medicine, with less than their proper share. Under the present system the long training required by medicine and dentistry is a further disincentive to recruitment to these professions

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[1] Grants to Students. Cmnd. 1051. H.M. Stationery Office. 1960. Pp. 136. 6s. 6d.

The case of the anti-abolitionists deserves respectful consideration A university education cannot, and should not, be offered to every citizen, should not then those who are able be asked to contribute to what is in effect a selective service? Are not parental contributions safeguards of self-reliance and self-respect for the citizen and of a small State-free income for the universities? Cannot too much importance be given to university education? May not some clever students lost to the university do the nation more good by climbing some other ladder? But even the minority group would like to see the parental contribution modified The amendments proposed would have the effect of reducing the present total parental contribution from nearly £5 million to £2 million And this reduction strengthens the case for abolition To be fair a system of contributions must be complex, and in practice administrative expense and effort might well become disproportionate to such a vestigeal remainder Furthermore the majority recommendation for the abolition of parental contributions proposes that parents should no longer be eligible for income-tax or surtax child allowances for students receiving awards With this proviso the committee estimate that the discontinuance of parental contributions would only cost the tax-payer an extra £1 million

Sir David Eccles has announced that the Government are to discuss the report as soon as possible with universities, local authorities, and schools, but he warned the House of Commons that even so the earliest date by which any new arrangement could be introduced would be 1961

DRUG-RESISTANT STAPHYLOCOCCI IN THE FARMYARD

SEVEN years ago regulations were made under the Therapeutic Substances (Prevention of Misuse) Act permitting the addition of penicillin and chlortetracycline to the diet of pigs and poultry The accelerated growth-rate of animals fed on diets containing antibiotics is well known (although the mechanism remains uncertain), and the economic advantages have led to the widespread addition of antibiotics—particularly tetracycline The wisdom of this procedure, in view of the possible development of drug-resistant infections in the animals, has been questioned, but, as we pointed out last year,[1] so far no disastrous results have followed

As was anticipated, changes in the bacterial flora of the intestinal tract have included not only a reduction in the numbers of certain species, notably *Clostridium welchii*,[2] but also the emergence of drug-resistant strains of *Escherichia coli*,[3] *Cl welchii*,[4] and probably other intestinal bacteria These findings have been largely disregarded, and indeed outbreaks of infection due to drug-resistant intestinal bacteria have not occurred

An unexpected and somewhat disturbing discovery, reported by Smith and Crabb,[5] is that pigs and chickens fed on antibiotics and also their attendants may become carriers of drug-resistant staphylococci

These workers compared the nasal and skin staphylococci of 160 pigs from sixteen herds which had been fed for one and a half to three months on a diet containing 10–20 g chlortetracycline or oxytetracycline per ton, with those of a control group of 160 pigs from sixteen herds not fed on antibiotics Of the tetracycline-fed animals 72% carried *Staph aureus* and 67% carried tetracycline-resistant strains In the control group the total carriage-rate was lower (57%) and tetracycline resistant strains were isolated from only 4% None of the strains isolated from either group was penicillin-resistant In a third, smaller, group of 38 pigs from four herds fed on diets containing penicillin 87% of the animals carried *Staph aureus* and 37% carried penicillin-resistant strains

Similar studies were made on 100 chickens from ten flocks that had been maintained for ten to eleven weeks on a diet containing 5 g procaine penicillin G per ton and 10–15 g chlortetracycline per ton, these were compared with a control group of 100 chickens from ten flocks not fed on antibiotics In the antibiotic-fed group 95% carried *Staph aureus*, and of a total of 492 strains isolated 41% were penicillin-resistant and 19% penicillin- and tetracycline-resistant In the control group a smaller proportion—58%—carried *Staph aureus* and of 246 strains isolated 3% were penicillin-resistant, 3% tetracycline-resistant, and 1% penicillin- and tetracycline-resistant

Finally the staphylococcal carriage of the attendants was studied Of 37 men looking after pigs not fed on antibiotics 35% carried *Staph aureus*, 5% carried penicillin-resistant strains, but none carried tetracycline-resistant staphylococci Of 35 men looking after tetracycline-fed pigs 57% carried *Staph aureus*, 11% carried penicillin resistant strains, 34% carried tetracycline-resistant strains, and 3% carried strains resistant to both antibiotics In a third group of 50 attendants of tetracycline- and penicillin-fed chickens the carriage-rates were total *Staph aureus* 48%, penicillin-resistant 30%, tetracycline-resistant 14%, penicillin- and tetracycline-resistant 4%

Study of the bacteriophage types of the tetracycline-resistant staphylococci showed that one type was predominant in each herd or flock and that, with the possible exception of one flock, staphylococci from the attendants belonged to the same phage type as those from the pigs and chickens

Thus, as in hospitals, both cross-infection and antibiotic administration appear to have played a part in the increased prevalence of drug-resistant staphylococci At least in the attendants the presence of antibiotic in the environment seems likely to have been a factor (Two years ago Gould[6] reported that this was an important cause of nasal colonisation of hospital staff with penicillin-resistant *Staph aureus*) Smith and Crabb suggest that the higher prevalence of tetracycline-resistant strains in pigs and their attendants may have been related to the fact that the pigs were fed on dry meal, which would more readily yield antibiotic-laden dust than the pelleted food used for chickens The analogy between hospital and farmyard is of considerable interest, but it cannot be assumed—and is perhaps unlikely—that the situation in the farmyard is potentially so dangerous

Nevertheless, whatever the danger for animals, a further source of drug-resistant staphylococci *in man* must give us pause, and a study by McDonald et al[7] suggests that the use of antibiotics in animal diets may have wider implications These investigators found a higher nasal carriage-rate of penicillin-resistant staphylococci in R A F recruits coming from rural areas than in those coming from towns They suggested that this might be associated with the drinking of unpasteurised milk from penicillin-fed cows, which may contain penicillin-resistant staphylococci[8] and small quantities of penicillin[9] A further explanation is that most people in rural areas have connections with farms, and that the recruits might, therefore, have had direct contact with penicillin-fed animals or their attendants It is noteworthy, however, that less than 0 5% of the recruits carried staphylococci resistant to tetracycline,[10] which was the commonest form of resistance recorded by Smith and Crabb

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[1] *Lancet*, 1959, i, 402
[2] Lev, M , Briggs, C A E , Coates, M E *Nature, Lond* 1956, 178, 1125
[3] Smith, H W , Crabb, W E *Vet Rec* 1957, 69, 24
[4] Smith H W *J Path Bact* 1959, 77, 79
[5] Smith, H W , Crabb, W E *ibid* 1960, 78, 243
[6] Gould, J C *Lancet*, 1958, i, 489
[7] McDonald, J C , Miller, D L , Jevons, P Williams, R E O *Proc R. Soc Med* 1960, 53, 255

THE CHESHIRE HOMES

"WHAT can't be cured must be endured" is a harsh but realistic saw, and, as our Disabilities series proved, people show almost unbelievable courage and resource in coming to terms with their handicaps and learning how to live with them The task is hardest for those who, despite all the help that improved methods of reablement can give, have to face a future in which they will always need some form of institutional care At present many of them are looked after in hospitals, where, even in a friendly ward, life must conform to a fairly rigid discipline that must fall heavily on the "resident" patient In his presidential address to the section of physical medicine of the Royal Society of Medicine on June 8, Dr Basil Kiernander reviewed sympathetically the needs of this group of patients and modern methods of helping them He described in particular the work of the Cheshire Homes for the Chronic Disabled, which from the smallest beginning have spread all through the United Kingdom and overseas There are now 16 homes in this country, with 8 more planned, 7 in India, 2 in Malaya, 2 in Poland, and 1 each in Nigeria, the Lebanon, and Jordan The first international home, called Raphael, has been started at Dehra Dun at the foot of the Himalayas and is to be expanded as a training centre and example of the ideal home

The Cheshire Homes vary according to local needs and local opportunities some are converted old mansions, while some are modern houses built with the advice of the patients But all encourage their disabled residents to lead a useful life and to help each other Often the patients have to retrain themselves in the simple activities of daily living as a patient put it, "all the little things that make you miserable when you cannot do them, like putting on your shoes, taking your soup, switching on the light" In the new home soon to be opened at Dulwich Dr Frank Cooksey and his colleagues are providing gadgets for a specially laid out kitchen

The experience of the twelve years since the first home was started by the Cheshire Foundation has suggested some general principles

About three-quarters of the patients in a home should need little nursing Not more than a quarter should be incapacitated by age or dying About 40 patients seems to be the best number With fewer, the home is an uneconomic proposition, with more, the atmosphere easily becomes institutional A preponderance of patients with any special disorder is unwise For instance, if more than half of the patients in a house have disseminated sclerosis there are temperamental difficulties It is unwise to mix the young and the elderly Some specialised homes have, however, been opened In India, for instance, there is need for homes for leprosy patients at different stages of the disease There is one home for mentally defective children in this country and another in India There is one home where patients who have left a mental hospital spend a few months before returning to their own homes

Each home is run by a small committee The members are local people and links with the outside world They invite the patients to their homes and make contacts with local industry The committee are responsible for the financial administration of the home and for the selection of patients for admission There is a matron or warden in charge of the home, but the patients share in the daily work of the home, helping with laundry, cooking, washing up, and looking after each other A welfare committee drawn from the patients run the funds, canteens, newspapers, and entertainments They are also encouraged to take up dressmaking, painting, manufacturing handicrafts, and printing as serious occupation The proceeds of the sales go to the welfare fund The running cost of the homes with the help of patients and volunteers has been kept as low as £6–7 a week per bed In each home two or three beds are reserved for disabled visitors who come while their families are on holiday or from other Cheshire Homes for a change

Dr Kiernander suggested that the hospital service might with profit study this independent experiment in helping the disabled to lead "not just an existence but a happy and useful life"

BIRTHDAY HONOURS

AMONG the new honours, we are glad to welcome first the name of Dr A M W Rae, chief medical officer of the Colonial Office, whose K C M G recognises devoted service beginning in West Africa in 1924 Air Vice-Marshal Rumball, who is promoted K B E, has not allowed his many other qualifications to diminish his distinction as a physician, and is a treasurer of the Royal Society of Medicine Of the new knights bachelor, Dr Robert Aitken left the regius chair of medicine at Aberdeen in 1948 to become vice-chancellor successively at Dunedin and Birmingham His chairmanship of the Committee of Vice-chancellors and of the Overseas Research Council bears witness to qualities long familiar to his medical friends Dr W E Chiesman has continued the tradition of wisdom and independence evident in Medical Advisers to the Treasury, and is president of the Association of Industrial Medical Officers Dr John Richardson, physician to St Thomas's Hospital, consulting physician to the Metropolitan Police, and editor of an interesting textbook, is a man whom his colleagues are always glad to consult Mr B W Rycroft, amid much ophthalmological achievement, has become one of the pioneers whose names are remembered, for many in years to come will owe their sight to his unceasing effort to make corneal grafting a generally practicable operation The knighthood bestowed on Mr Douglas Robb comes happily at the beginning of his visit to Britain as Sims professor of surgery Thoracic surgeon, pro-chancellor of the University of Auckland, and president-elect of the British Medical Association, he is notable also, and especially, as a person Also in Australasia, Lady Herring is created D B E for her welfare work particularly in nursing organisations in Victoria, where her husband is Lieutenant-Governor

The list appearing on p 1342 contains many other names which are already honourably familiar in the profession

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Dr ALEXANDER KENNEDY, professor of psychological medicine in the University of Edinburgh, died on June 11 at the age of 51

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[8] Tee, G H *Mon Bull Minist Hlth Lab Serv* 1957, 16 141
[9] Panes, J J, Edge, M., Hobson, M, Thomas, S B *J Soc Dairy Tech* 1957, 10, 81
[10] Williams, R E O Personal communication

Public Health

A POLIOMYELITIS EPIDEMIC IN GREECE

Gunnar Gille
M D
DEPUTY HEAD OF THE HOSPITAL FOR CONTAGIOUS DISEASES,
STOCKHOLM, SWEDEN

Before 1949 only sporadic cases of poliomyelitis were encountered in Greece, and these were practically never in the acute stage, though the sequelæ—i e, flaccid paralyses—were occasionally seen in children The prevalence of paralytic cases since 1949 is shown in fig 1

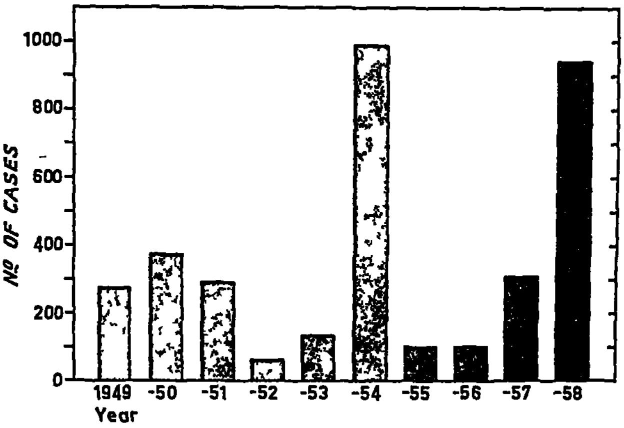

Fig 1—Prevalence of paralytic poliomyelitis in Greece, 1949-58

In the past 10 years there have been usually not less than 100 cases of paralytic poliomyelitis a year In 1954 the paralytic cases numbered about 1000, and these were chiefly in the northern regions Most of the patients were less than three years old, and the mortality-rate was below 4%

The Epidemic

A serious outbreak of poliomyelitis began in May and June, 1958 In June some 200 patients were treated at the children's clinic in Athens, and the mortality in this group was 20% The Greek Red Cross appealed for help from the International Red Cross League, and I was sent to Greece as delegate of the Swedish Red Cross to report on the situation and to assess the help required

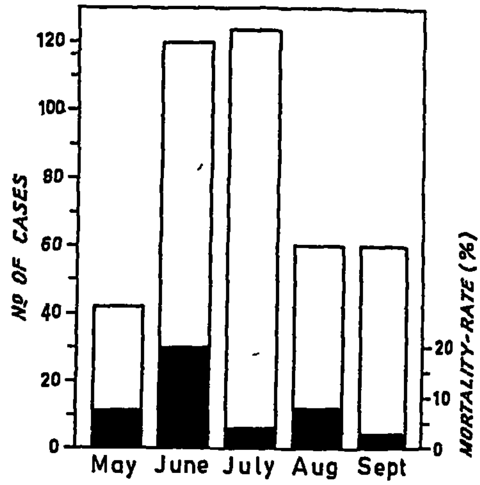

Fig 3—Cases of paralytic poliomyelitis treated in Athens hospitals and the fatalities, from May to September, 1958.
The respiratory unit started work at the beginning of July

The children's clinic in Athens was faced with enormous problems through lack of equipment and trained staff—and especially those with knowledge of respiratory treatment. Suction of the airways, systematic turning of the patient, and postural drainage were not practised Consequently many patients got pulmonary complications

The immediate need was clearly of a department in which the primary treatment would be to keep the airways free and to standardise the electrolytic and caloric intake A respiratory department requires, above all, trained staff, and it also needs technical equipment Both were promptly sent by the Swedish Red Cross Two poliomyelitis nurses arrived, followed by a physiotherapist, from the Stockholm hospital for infectious diseases Various respirators, suction pumps, and other equipment were given The German Red Cross sent two Drager tank respirators

A respiratory department, the first in Greece, was established at St Barbara's Hospital in Athens (the hospital for infectious diseases) Fresh cases of poliomyelitis were admitted to this department from the surrounding area and from remote parts of the country But the technical resources at St Barbara's were very limited, and only emergency action could be taken. I was therefore unable to make a clinical classification of the patients

As soon as the respiratory department was established it was filled with patients, and from July until January, 1959, some 500 cases of poliomyelitis, all paralytic, were treated Practically no non-paralytic cases were seen A questionnaire was sent to doctors in the province of Argolis in the Peloponnesos, one of the most severely affected areas, but none reported widespread outbreaks of headache or fever Many people must have considered these

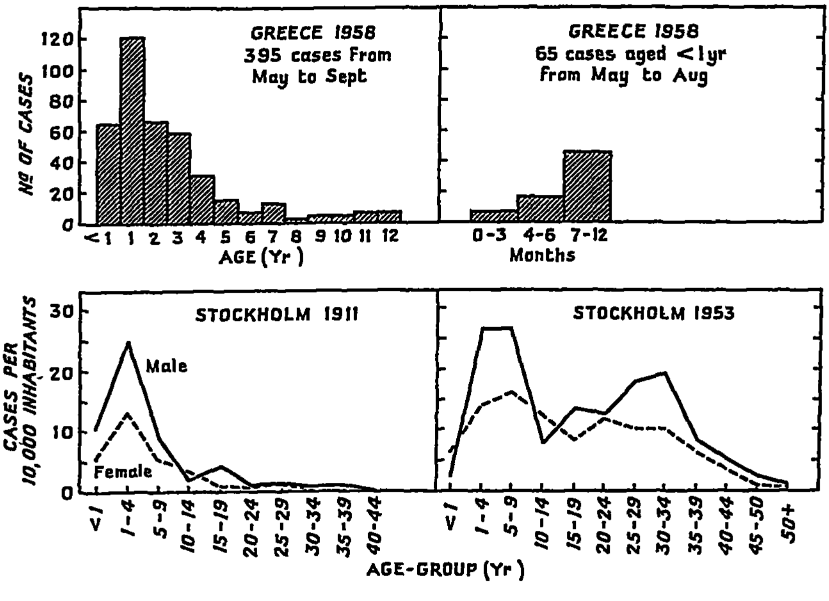

Fig 2—Age and sex distribution of cases of paralytic poliomyelitis in the 1958 Greek epidemic compared with the 1911 and 1957 Stockholm epidemics (according to Ström [1])

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[1] Ström, J *Acta med scand* 1956, suppl 316, 10

symptoms too slight to warrant a visit to a doctor And doctors, when consulted, did not suspect poliomyelitis, because the non-paralytic form is unknown in Greece. Lumbar punctures were not usually performed, although a few were made on suspected non-paralytic cases, all of which proved to be positive The non-paralytic form naturally occurs though the diagnosis is more difficult in infants than in older children and adults

Fig 2 shows the age-distribution of the paralytic cases compared with that in the outbreaks in Stockholm in 1911 and 1953 There were also 4 adult patients, 2 of whom were tourists from Sweden and West Germany Severe bulbar poliomyelitis has never been seen in Sweden among children under two years of age But in the Greek epidemic, in which nearly all patients were infants, a few did contract the severe bulbar form, and among these several died Probably most of them had such severe lesions in the central ganglia that recovery was impossible, yet a few would probably have survived had the conditions been more favourable. Fig 3 shows the total number of cases, and the mortality-rate month by month.

The overall mortality-rate among 500 patients was 5%, but this figure represents some selection since mild cases were treated elsewhere In its usual way, the illness increased rather than decreased in severity during the course of the epidemic. Rather more than half the patients required some form of respiratory treatment for various periods Fortunately respiratory insufficiency and dysphagia were overcome by simple means such as suction, postural drainage, and body respirators

The Swedish Red Cross assistance lasted from the end of June to October, 1958 The number of new cases gradually diminished until February, 1959, after which no further cases were reported

Discussion

The Greek poliomyelitis epidemic in 1958 prompts reflections on the state of immunity in the country The age-distribution and the relatively few cases—about 1000 paralytic cases in an overcrowded area with 8 million people—suggest that the immunity is generally satisfactory Since the epidemic it should, of course, have improved Moreover, geographically practically no part of the country was spared, the patients coming from all provinces and island groups (fig 4 shows the number of paralytic cases from different parts of the country)

Under the circumstances mass vaccination seemed pointless If, by virological methods, it were possible to discover any groups of people who were not immune, they should be vaccinated But this seemed improbable in view of the regular communications between different areas Within a few years' time the infants may again be exposed to infection If the virus is present in large amounts under conditions which favour its spread, the intervals between epidemics might be shorter than is usual in the Scandinavian countries Fig 1 might suggest a free interval of four years If that is correct, it would be advisable to vaccinate the youngest children within a year or two The living, attenuated virus method, which seems to be " around the corner " would be best for this purpose A single dose by mouth must be the ideal method of mass vaccination in a country such as Greece

Another threatened group of individuals is tourists from countries with a low immunity They should be

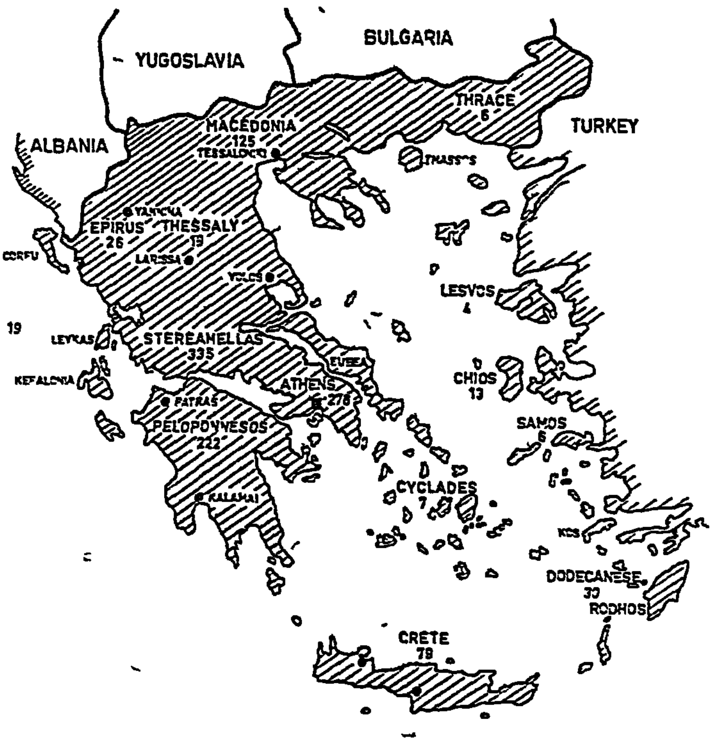

Fig 4—Geographical distribution of cases of paralytic poliomyelitis

vaccinated beforehand. Non-vaccinated tourists should be given γ-globulin.

With regard to social distribution, though I cannot prove it by statistics, the youngest patients undoubtedly were predominantly very poor The few older patients came mostly from higher social groups

I am indebted to the Swedish National Association Against Poliomyelitis for financial aid

Outbreak of Syphilis

An outbreak of syphilis in Maryland has been described by Bird and Cornish.[1]

In June, 1959, primary syphilis was diagnosed in a 29-year-old man. Intensive investigation of his contacts and associates, involving examination and blood-testing of over 300 persons, led to the detection of 44 previously unknown cases of syphilis, 28 of these had primary or secondary syphilis, 14 had early latent syphilis, and 2 had late latent syphilis 31 of the cases were found in three counties on the Eastern shore of Maryland, 7 in four other Maryland counties, and 6 in Delaware and Florida.

26 of the 28 found to have primary or secondary syphilis who were living in Maryland were interviewed and named a further 124 contacts, 47 of whom were found to have syphilis, 23 had had no treatment, and 15 of these had acquired the disease recently and were in the primary or secondary stage 12 of the 14 with early latent syphilis named 56 more contacts. 16, of whom 5 were not already under treatment, had syphilis, 2 of the 5 had primary or secondary syphilis and 3 early latent syphilis

Most of the original 44 were from the lower socioeconomic strata, few were regular school attenders or had permanent employment. All but 4 were under 25 years of age, and 25 were under 20, a girl of 13 being the youngest. The oldest patient was 37 All were non-whites, an admitted prostitute named several white men as contacts, but none of them was infected. Those involved were promiscuous, one 17-year-old girl, for example, having had intercourse with 22 different men in six months

A case-finding method called "cluster testing" was used, involving investigation not only of sex contacts of patients, but also of friends and associates who might have been exposed—including, for example, the patrons of a bar frequented by many of those involved

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[1] Bird, C. D., Cornish, T L. *Maryland Dep Hlth news Bull* 1960, 32, no 2.

This outbreak occurred in a stable and progressive community with good medical and public-health facilities It points to the continuing need for an active control programme even in areas assumed to have a low prevalence of syphilis

Food Additives in America

In the United States the cherished principle that the accused is innocent till proved guilty no longer applies to food additives Hitherto the Food and Drug Administration have had to prove a material dangerous before banning it, but since March there has been a ban on any material not authorised The Administration published a list of 453 such substances " generally regarded as safe ", in other cases the manufacturer must ask the Administration for specific clearance or must file a petition (with evidence that the substance is harmless) for regulations prescribing its use This shift in the burden of proof involved the food industry in a great deal of work in obtaining the required evidence, and many firms asked for grace [1]

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[1] *Christian Science Monitor*, Feb 25, 1960

Infectious Diseases in England and Wales

Disease	Week ended May			
	7	14	21	28*
Diphtheria	2	1	2	2
Dysentery	1096	1038	1151	1312
Encephalitis				
Infective			4	4
Postinfectious	4	2	1	1
Food-poisoning	121	156	151	157
Measles, excluding rubella	1575	1752	1886	2254
Meningococcal infection	14	15	20	25
Ophthalmia neonatorum	31	24	21	21
Paratyphoid fever	4	2	12	3
Pneumonia, primary or influenzal	292	290	250	256
Poliomyelitis				
Paralytic	7	1	2	6
Non-paralytic	3	2	5	6
Puerperal pyrexia	143	178	209	196
Scarlet fever	533	593	624	606
Smallpox				
Tuberculosis				
Respiratory	416	457	464	459
Meninges and C N S	4	9	3	8
Other	52	53	64	61
Typhoid fever	1	2	1	3
Whooping-cough	1201	1362	1458	1453

* Not including late returns

Special Articles

BIRTHDAY HONOURS

The list of honours published on June 11 contains the names of the following members of the medical profession

K C.M G.

Alexander Montgomery Wilson Rae, C.M G , M D Edin
Medical adviser to the Secretary of State for the Colonies

K B E (Military)

Air Vice-Marshal Campion Aubrey Rumball, C B E , F R C P , Q H P

D B E.

Mary, Lady Herring, M B Melb
For social welfare services, especially with the nursing organisations of Victoria

Knights Bachelor

Robert Stevenson Aitken, M D N Z , LL D , D SC , F R C P
Vice-Chancellor, University of Birmingham

Walter Eric Chiesman, C B , M.D Cantab , F R C P
Medical Adviser, H M Treasury

John Samuel Richardson, M V O , M D Cantab , F R C P
Physician, St Thomas's Hospital, London

George Douglas Robb, C M G , M D , CH M , B SC , N Z , F R C S , F R A C S
Consulting surgeon, Greenlane Hospital, Auckland, New Zealand

Benjamin William Rycroft, O B E , M B St And , F R C S
Ophthalmic surgeon, Queen Victoria Hospital, East Grinstead

C B. (Military)

Major-General Gilbert Thomas Lancelot Archer, M B Dubl , F R C P I , Q H S

Major-General William Dillon Hughes, C B E , M D Belf , F R C P I , Q H P

Surgeon Vice-Admiral William Robert Silvester Panckridge, M R C S , Q H P

Surgeon Rear-Admiral Dermot Francis Walsh, O B E , M B Dubl , F R C S E , Q H S

C B E (Military)

Brigadier Leslie Reginald Heber Keatinge, O B E , M B Dubl , late R A.M C

Air Commodore Gerard Ward McAleer, M B N U I , Q H P , R.A F

Colonel John George Glynn White, O B E , E D , M B Melb , R.A A M C

C.B E. (Civil)

David Brown, M B Lpool
For political and public services in Bootle

Lawrence John Clapham, M D Lond
Director of medical services, North Borneo

James Graham, M A., M.B Edin
Senior administrative medical officer, North East Metropolitan Regional Hospital Board

Ian Dingwall Grant, M B Glasg , Hon M D Birm
Lately president, College of General Practitioners

Ludwig Guttman, O.B E., M D Freiburg, M R C P
Director, National Spinal Injuries Centre, Stoke Mandeville Hospital, Aylesbury

Henry McLorinan, M B Melb , F R A C P
Medical superintendent, Fairfield Hospital, Victoria.

Martin Amsler Rushton, M D Cantab , F D S R C.S
Professor of dental medicine in the University of London at Guy's Hospital

M V O (Fourth Class)

Wing-Commander Herbert Brian Kelly, M D Lond , R.A.F

O B E (Military)

Surgeon Commander Clifford Vivian Harries, M R C.S , R.N

Surgeon Commander Robert Adams McKeown, M.B Belf , R.N.R.

Wing-Commander John Erskine Malcolm, M B St And , R.A.F

O B E (Civil)

John Adam, M B Glasg
Regional medical officer, Ministry of Health

Wladyslaw Dering,
Senior medical officer (surgical), Somaliland Protectorate.

John Dixon, L R C P E
Chairman, St Albans medical board

Hugh Richard Jarvis Donald, B M Oxon
Physician, public hospital, Christchurch, New Zealand

Cyril Fortune, M D Melb , F R.A C P
For services to the blood-transfusion service, Western Australia.

Geoffrey Desmond Gordon, M R C S
Senior medical officer, Ministry of Pensions and National Insurance

Robert Fritz Herries Hinrichsen, M D Brazil, F R C S
Medical director, Strangers' Hospital, Rio de Janeiro

Leonard Catesby Huggins, M B Edin
Medical officer and bacteriologist (senior surgeon), Bahamas

Trevor Claude James, M B Melb
Commissioner, St John Ambulance Brigade, Tasmania.

Winifred Barbara Meredith, M B Melb
Director, maternal, infant, and preschool welfare, Department of Health, Victoria

THOMAS McCOWAT MONTFORD, M.B. Glasg.
Chairman, Leicestershire and Rutland executive council

MILES PARKES, M.B. Manc.
Vice-chairman, Cheshire executive council.

CHARLES EMANUEL WILLIAMS, M.D. Melb., F.R.A.C.S.
Medical practitioner, Mackay, Queensland

M.B.E. (Military)

Surgeon Lieut.-Commander DONALD CAMPBELL McNUTT, M.B. Edin., R.N.

M.B.E. (Civil)

LEONARD EDWARD ARNOLD
Pathologist, police department, Jamaica.

HECTOR MACKAY CALDER, D.S.O., M.C., M.D. Glasg.
Lately member, Glasgow National Service board

WALTER WATSON FEATHER, M.B. Sydney
Medical superintendent, Roma hospitals board, Queensland.

THOMAS DUNCAN GOULD, L.R.C.P.E., L.D.S.
British subject resident in Brussels

MARY RAE KEYMER, M.B. Glasg.
Honorary physician, C.M.S. Hospital, Omdurman, Sudan.

MURIEL MILLICENT MANLEY, M.B. Lond.
Medical Officer of health, Kingston, Jamaica.

EDWARD HAMMOND WILLIAMS, M.B. Lond.
Medical superintendent, Kuluva Leper and General Hospital Arua, Uganda.

THE SOVIET MEDICAL SERVICES

THE purpose of the World Health Organisation's "public health paper" on Soviet Russia,[1] as of others in this new series, is to stimulate international thinking, discussion, and planning. It was prepared by medical and public-health representatives of 21 different countries (not including Western Europe or the United States) who, in October, 1958, made a five-week tour in the U.S.S.R., organised by W.H.O.

Clearly written with well-arranged headings, it is based on an official publication of the U.S.S.R. Ministry of Health, and it describes the structure of the Russian health services after 40 years of development, experience, and research. The object of the complex but unified organisation is to provide comprehensive medical care for the whole population, with central supervision but peripheral operational freedom, and integration of prevention and treatment. The three main sites of medical care are (1) central highly specialised institutes, (2) city hospitals, with policlinics and district units attached, and (3) rural hospitals, connected with district hospitals and policlinics. Diagrams at the end of the report illustrate clearly the structure of the medical services as a whole and also of a rural medical district, of a city hospital, and of a factory medical and sanitation department.

The separation of adult from child medicine (and of hygiene from both) is described, together with other striking characteristics of Soviet medicine such as the large amount of time and money spent on "prophylaxis" and on physical methods of treatment in rest homes and health resorts. The hours worked by doctors and nurses, the number of hospital beds for different specialties, the importance attached to maternal and child health, occupational health, and sanitation, and the special provision made for infectious and chronic illness are also mentioned.

Six pages are allotted to medical education (undergraduate and postgraduate), two to the training of nurses, midwives, feldshers (assistant doctors), and technicians, three to health education of patients, two to research, and one each to mental health and vital statistics. A doctor now visiting Russia tells us that he found the booklet very useful as an introduction to what he was to see.

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[1] Health Services in the U.S.S.R. World Health Organisation public health paper no. 3. 1960. Pp. 58. Obtainable from H.M. Stationery Office, 3s. 6d. Also published in French.

Occasional Survey

"FAULTS", "HITS", AND AGEING

THE PROCESS by which we—and other animals—lose vigour with age has an attractive mathematical regularity. This may be advantageous for life assurance but it is also responsible for a vast number of attempts to settle mathematically a problem which in the long run, can be settled experimentally and in no other way; most of them made by *savants calculs* of a metaphysical cast of mind, or by mathematicians without biological experience. This historical background accounts for the exasperation with which experimental gerontologists are apt to regard speculative papers explaining ageing in terms of the shape of the survival curve, and the apprehension with which many view the latest irruption of physicists into the subject, following the discovery that low doses of radiation appear to accelerate ageing.

The most recent of these mathematical attempts, by Szilard,[1] evokes some of these reflex responses, but it differs radically from the *savant calcul* tradition in identifying mathematical properties with tangible and measurable biological facts, and in suggesting experiments to verify the speculation. In the face of the evidence from radiation experiments[2] some such theoretical attempt had to be made, and gerontologists conducting survival studies have been looking at their results to see how far Szilard's theory fits them.

Szilard starts by assuming that the elementary step in the process of ageing is a "hit" (not necessarily by a radiant particle) which renders all the genes on one chromosome of a somatic cell inactive. "Hits" are random events, the probability throughout life of any one chromosome being "hit" is constant, but the rate of occurrence of "hits" is characteristic of the species. As a result of these "hits" the proportion f of somatic cells which are still functioning properly declines with age, until it reaches a value f^*, at which point the probability of dying within the next year approaches unity.

At the same time, every individual is assumed to carry a load of genetic "faults". A "fault" is a mutation in one of the genes essential to the proper working of a somatic cell. (In man, Szilard assumes that 3000 out of a probable 15,000 genes are essential in this way.) A cell ceases to be able to function when both members of the gene-pair for any one of these "vegetative" genes are out of action. Accordingly, when a chromosome suffers a "hit", the cell will cease to function (a) if the homologous chromosome has already suffered a "hit", or (b) if it carries the corresponding "fault" at a vital point.

This then, is the model. By assuming probable values for quantities which nobody knows, Szilard proceeds to derive plausible approximations to the observed values of quantities which we do know, such as the concordance between twin ages of death. He also proposes, not an experimental proof, but a critical experiment—the reduction of life-span in the F_1 born to irradiated male mice, which was observed after some of the American bomb experiments,[3] could support or negative the mathematical model.

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[1] Szilard, L. *Proc. nat. Acad. Sci.* 1959, 45, 30.
[2] Comfort, A. *Radiation Res.* (Suppl.) 1959, 1, 216.
[3] Russell, W. L., Russell, L. B. ibid. p. 296.

The model itself has a number of other important implications One is that if m, the number of chromosome pairs, is different for two different species, the specific life-shortening due to a dose of radiation will be greater for that in which m is the smaller, and will vary inversely as $\sqrt{m}$ Szilard also works out, on the assumption of an average in human females of $n = 2\ 5$ inherited "faults" per head, the modal longevity of a genetically perfect female with no such "faults" it comes to 92 as against the present 80 years If n were greater it would be more He also concludes that at the gloomiest estimate the load of "faults" cannot double in less than 25 generations from any cause, for $n=2\ 5$ this doubling would represent a loss of longevity of 15 years

As Ernie Pyle would say, "the first word which comes to mind is But"—particularly to biologists working on age processes and aware of their probable complexity At the same time, this kind of mathematical simplification cannot be rejected out of hand, because it has often worked surprisingly well—Morgan's assumption that the genes on a chromosome are arranged in a straight line and behave accordingly is a case in point Such models can cut the Gordian knot or merely tangle the subject further The essential for Szilard's model to be relevant seems to be that ageing should be timed by a fault in replication following the loss of an allele which is essential to a single cell If his model fits universally, or at least well, and goes on doing so when "probable" are replaced by observed quantities, it would support this idea The two most immediate criticisms were made almost as soon as the theory appeared,[4] and answered, or accommodated, by its author The first is that if the theory of "faults" is correct one might expect the vigour of inbred and homozygous animals to be greater than that of hybrid or heterozygous animals, whereas the reverse is almost universal The second concerns his "probable" values The only reason for Szilard's assumption that a "hit" inactivates one whole chromosome seems to be the need to find a quantity of the right order of magnitude to account for the difference observed, for example, between male and female longevity, there being too many genes and too few cells to yield sensible results, while the human chromosome number is conveniently situated between the two

It is also difficult to relate Szilard's theory as it stands to the dynamics of cell-division, for it makes no distinction between the effect of chromosomal "hits" developing in cells of which the population is fixed from birth, in high-turnover cells, and in stem cells where "faults" acquired by point mutation and "hits" will both affect cellular progeny Vertebrates are a mosaic of all three types of cell If Szilard's critical proportion f^* represents a fraction, not of the cell numbers but of an unspecified stuff "vitality", his further equations only restate the accepted actuarial pattern in different terms to make them experimentally useful, ageing must be timed predominantly by loss of irreplaceable postmitotics—neurones, perhaps, or endocrine cells unspecified, or by a process with the same mathematical properties The idea of ageing by essential cell loss is an old one it can by no means be excluded as a cause of mammalian ageing, while for the ageing of forms such as insects, which have a low cell turnover, or rotifers, which have none, it seems very probable It might also apply to special organs or contexts (Szilard's "special vegetative" processes) which contribute to ageing by their failure it already looks, for example, as if the senescence of the human ovary may be due to running out of oocytes

If human ageing were indeed timed by the loss of key postmitotics, the Szilard theory would become at least plausible The effects of radiation which are said to accelerate ageing must then presumably be on postmitotic chromosomes or their products—a subject on which nobody seems to have much information But as a rule non-dividing cells, and animals composed of them, are notoriously insensitive to radiation damage In this respect the word "hit" is misleading, however, because of its radioactive implications *Loss*, or rather constitutional absence, of a chromosome has become a more familiar concept in the last few months than ever before, with the discovery of human aneuploids suffering varying degrees of disability If, as the equations seem to require, the unit of a "hit" is a whole chromosome, loss, or some other non-radiological disaster which might not be visible, is a more likely expectation If neurones or the like are involved, there are in any case no outward and visible chromosomes in the mitotic sense to be hit, and the process envisaged must be analogous to the decay of teeth in the Cheshire Cat's grin

There is another and far more interesting possibility, however, involving mutation in its more usual sense and confined to a single cell system, to which Szilard's mathematical intuitions might possibly be found to apply Immunologists now seem to accept that the power to produce each individual antibody is acquired initially by an individual lymphocyte and transmitted to its progeny A mechanism, not fully understood, determines that lymphocytes shall not normally respond to their proprietor's body-constituents by forming antibodies against them Burnet has recently suggested[5] that if mutation in lymphocytes is capable of affecting this negative specificity, the organism must face a steady increase in autoimmune reactions with the passage of time—reactions which are likely to be of precisely the variable, diffuse, and polymorphic type which might explain the natural history of ageing as seen in man, while the statistical constancy of the mutation-rate and/or the rate of occurrence of Szilardian "hits" remains to provide the basis of life assurance

This idea, that the organism comes with time to have more and more cells producing substances inimical to its own tissues, is an unexpected revival of Metchnikov, who always predicted that the same cellular mechanisms would turn out to be morphogenetic in the embryo, immunoprotective in the adult, and actively destructive in the end The application of Szilard's scheme to such a system calls for some thought, but it appears at first sight to fit rather well, or at least better than most The effect of a "hit" is in this case not that it removes a cell from useful activity, but that it puts one, and probably also its progeny, into destructive activity, and f^* is no longer a proportion of an original cell capital below which we are bankrupt, but something more like a median lethal dose Meanwhile, Burnet's theoretical argument demonstrates quite plausibly that something of the kind ought to take place What is still lacking, however, is experimental evidence that it really does so

ALEX COMFORT

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[4] Maynard Smith, J *Nature, Lond* 1959, 184, 956, Szilard, L *ibid* p 958

[5] Burnet, F M Croonian lectures to the Royal College of Physicians, 1959

In England Now

A Running Commentary by Peripatetic Correspondents

THE retired G.P. will find numberless uses in the garden and the house for the tools of his trade. Forceps of various types for picking out seedlings or retrieving dentures, rings, and other precious objects from "down the plug-hole", "cut-throat" razors for layering or grafting, tourniquets for fractured boughs, and so on. Some weeks ago a blue tit began to build in the wooden letter-box of our weekend cottage, as it had done in two previous springs, in spite of a perfectly good nesting-box alongside and arrowed notices "Tits here", and "Letters here"—one would almost think they could not read. Two weeks later there were eggs, but a letter had meanwhile been delivered and incorporated in the nest. I was concerned about the letter and my wife about the disturbance to the nest which its extraction would inevitably cause. The problem was solved by examination with a laryngeal mirror which revealed a brown twopenny stamp. Clearly we need lose no sleep over a receipt or a demand for the rates. The Uckfield R.D.C. or the P.M.G. could surely wait, and meanwhile the postman obligingly put other communications under the door. Alas for human ingenuity and cooperation! Last weekend the door of the box stood open, the nest was scattered over the lawn—the letter proved to be an advertisement for Shetland wool with samples—and two moribund young tits were all that remained of the family. It was late evening and the remnants outside were cleared up and the door of the letter-box shut on what was left and on the young tits, now dead. Next morning the door was open, the bodies had vanished and the remaining nesting materials scattered around. Was it some Ruthless Rat, some Faceless Chinese Badger, or (my own theory) a Pockmarked Mexican Grey Squirrel?

* * *

"You told me there would be nothing to it, doctor, just a small operation, you said. You didn't tell me about the night before, with me lying there and my heart thumping, listening to the coughing and the snoring, and watching the nurses at the end of the ward. It was just light when they came and took my teeth out, and took my rings off and me worn them night and day for these last thirty years. Then they put me on a cold, stiff nightdress. 'No breakfast for you this morning, dear,' they said. The other patients drank their tea and smiled. 'You'll be all right. There's nothing whatever to worry about. Well good luck anyway,' they said. 'Come along there, Nurse Binks,' said the sister, 'you should have had her away half an hour ago.'"

* * *

When I admit a woman from outpatients I have often had to ask the Almoner to find somebody to look after half a dozen small children, but last week's patient said "I run a riding-school single-handed. Who will look after my twenty horses, three cows, and a dog?" The Almoner had no idea which end of a horse was which, and she could think only in terms of children's homes. So I had a rapid course on breast-pumps from the Obstetrician, and the problem of the milking of the cows seemed to be settled. My small daughters have a pony and it was, therefore, decided that, as an expert on the feeding and mucking-out of one small riding pony, I could easily look after twenty horses.

Fortunately, the patient was able to go out in a couple of days, and I can now appear in the hospital without straw in my hair and no longer smelling too strongly of the gardener's friend!

* * *

Today I saw a lorry that came from Denton. It took my mind back to the days when I worked in Manchester and had my car serviced in Denton at a remarkable garage which had evolved from the local smithy. It was full of anvils and old cartwheels, and there was an open fire in the middle of the floor. The owner was unsuitably named Clarence; he was a tough, stocky, curiously old-fashioned fellow who had a fund of wise saws. If I complained of a noise in the engine, he would say: "Ah well, where there's noise there's power".

Once, when a three-day job was needed on my car, I asked Clarence if he would lend me one in the meantime. Those three days must have narrowed my coronaries considerably. The ancient car had no brakes at all, only two gears (first and fourth), and no lights to speak of; but there was a system for "audible warning of approach". To sound the horn, you picked up a piece of wire that hung loose from the dashboard and applied the end of it to any convenient piece of metal. I was scared stiff of electrocuting myself.

When I turned up at the end of the third day, Clarence showed signs of relief. I imagined he had feared for my safety, but I was wrong. "Y'know," he said, "I'm right glad to see you. I was beginning to feel ashamed to think of a doctor riding about in yon. It oughtn't by rights to be on the road at all." The respect that he put into the word "doctor" came straight out of the 19th century. It made me think I should be inquiring whether he'd finished the work on my buggy.

* * *

Looking through my small daughter's exam-papers I came on a thing called a gerund. It seems to have something to do with parts of speech, and I can swear it was no part of anything in my day. I had never heard of it before. Fishing for information I remarked that "you don't see many gerunds around nowadays", and when this produced no reply I tried "I think they've given up gerunds on the telly." Retiring baffled I tried my wife with "They do teach gerunds very early nowadays", and only got a cold look for my pains. Deciding to play this game more dodgy-like, I tried the public library with "a book on parts of speech please", to be met with "which part would you like?" This was a teaser as I always thought there was only one part. However, as a final gambit I managed a "which part do you usually have?" This was stalemate with honours even. Next time I'll go it alone. If I start with autobiographies and work my way through hobbies to geography, by this time next year I should have struck oil and gerunds.

* * *

It isn't always an advantage to have a brother ahead of you in medicine. Brother George, two years my senior, once said to me, "Now, Bill, some time in the biology class the lecturer will announce, 'Today, we are going to study the botany of the apple, the berry, the rowan, and the haw.' You be ready for him and shout out, 'Haw, Haw.'" I thought that would be great fun and eagerly awaited the day. At last it came, and as George had predicted the lecturer, with seeming deliberation, said, "Today we are going to study the botany of the apple, the berry, the rowan, and the haw." He seemed to pause, so that I had plenty of time to shout out "Haw, Haw." After the laugh had died down he said, "Ah, yes, the annual donkey."

However, I got my own back on brother George. I followed him into a house job and also into his place in the pack of the local rugby team. I played well in my first games and the local newspaper published a note about my play in the sports column. I sent it, with love, to brother George. It ran, "Dr P— is having his second season with the town team, and is a greatly improved player from the form he showed last year."

* * *

A MATTER OF TIME

So, here you see me. Cast away
My brief Combustion ended, all my Fire
In one last plume of Smoke must now expire.
Others have been before me, said their say,
Have kissed those self-same Lips this very day
And gone; his Breath will yet inspire
A Dozen others like me. Not Desire
But mutual Death is in our fleeting Play!

What though he is the Master and 'twas Men
Created us, the lesser partners in the Game?
It is too early yet for him, poor Fool, to boast,
A Hundred Thousand of us may be Ash by then.
But Twenty years from hence it will be all the same—
And who, I wonder, will have lived to suffer most?

Letters to the Editor

"METABOLIC INSUFFICIENCY"

SIR,—Your editorial,[1] Goodbye to "Metabolic Insufficiency" made the strong inference that the last word had been written concerning this controversial syndrome, and further investigation had better be abandoned lest euthyroid hypometabolism (a preferable title) be denied its "quiet disappearance from the medical literature" Unfortunately the argument cited, the report by M E Levin—based on a "double-blind" study conducted on only 6 patients—hardly supports such a decisive stand

One might gather from the editorial comments of several of the medical journals that the "double-blind" study has become a modern-day Holy Grail, relegating less ambitious researchers to ignoble ends Be this as it may, one all-important factor which must be firmly established—particularly when a hormone is used in a "double-blind" study—is proper and adequate dosage One can easily imagine the opportunity which might have been missed had Best and Banting decided to put 5 units of insulin to the "double-blind" test in the treatment of diabetes One might also recall the erroneous conclusions reached in the British study comparing salicylates and cortisone (100 mg) in the treatment of acute rheumatic fever The experience of Kurland, Hamolsky, and Freedberg, as well as my own in 32 cases, has clearly shown that the majority of "hypometabolic" cases require a minimum daily dosage of 100 μg triiodothyronine, and even then there is usually a time lag of two or three weeks before subjective or objective improvement is observed Thus, considering that a final dosage of 75 μg was given by Levin, and this for only two weeks in one-third of patients and four weeks in two-thirds, it is hardly surprising that his results were equivocal The time-lag in the euthyroid hypometabolic patient before triiodothyronine affects the basal metabolism is in striking contrast to the prompt metabolic response to triiodothyronine in three to five days in cases of true hypothyroidism

During the past three years, approximately 500 patients have been screened in our endocrine clinic for euthyroid hypometabolism, the majority of them were suspected of being psychoneurotic or hypothyroid Among this group, 32 patients (6 4%) were believed to have euthyroid hypometabolism as judged by the following diagnostic criteria

(1) A symptom-complex resembling hypothyroidism in certain respects and psychoneurosis in others

(2) Presumably normal thyroid (thyroxine) function as shown by a normal protein-bound iodine value (P B I) and a normal rise in P B I following the administration of thyrotrophic hormone

(3) Objectively, a B M R below minus 10% and a prolonged electrometric recording of the free Achilles reflex [2]

(4) No response to placebo or desiccated thyroid, the latter given in daily dosages up to gr 5 or intolerance

(5) A favourable response, both objectively (B M R and reflex recording) and subjectively, to proper amounts of triiodothyronine—on the average of 100–125 μg daily—and maintenance of such improvement over a minimum follow-up period of six months

Previously a major drawback to screening patients for hypometabolism has been the absence of an objective parameter of end organ metabolism, which is consistently abnormal in such cases, and of a higher degree of accuracy, reliability, and reproducibility than the conventional B M R procedure (Only 50% of B M R s were abnormally low in these 32 cases when done for the first time The majority of patients had B M R s recorded on three consecutive days) This situation has been remedied by the finding that the contraction phase of the Achilles reflex (as measured electrometrically by the Lawson apparatus) is significantly prolonged in both hypothyroidism and euthyroid hypometabolism in over 90% of cases, and that such an abnormality is only rarely encountered in other diseases affecting metabolic or neuromuscular function Furthermore, neither the B M R nor reflex recording shows improvement in truly euthyroid hypometabolic patients given desiccated thyroid or placebos or positive suggestion, but returns to normal levels when triiodothyronine in adequate doses is given Since the "hypometabolic" patient often masquerades clinically as a psychoneurotic and is usually misdiagnosed as such, and since triiodothyronine is completely effective in relieving the so-called "psychoneurotic" complaints in the vast majority of "hypometabolic" patients, it seems well worth screening such patients for hypothyroidism or euthyroid hypometabolism and thus spare them the fate of the true neurotic—dependence on tranquillisers or prolonged expensive psychotherapy

The relationship between euthyroid hypometabolism and "neurotic" behaviour is probably more than a casual one, although a precise cause-and-effect mechanism remains unknown In fact, considering that all the tests of the functional capacity of the thyroid gland itself (in contrast to end organ metabolism) have been found to be within normal limits in the euthyroid hypometabolic patient, the possibility remains that this syndrome is not a thyroid disease at all, but results from some cortico-hypothalamic factor or bodily dysfunction which affects the thyroid gland—particularly the formation and release of triiodothyronine—only secondarily, as happens, for example, in hypopituitary myxœdema In summary, it is my present belief and experience that a syndrome of euthyroid hypometabolism does, in all likelihood, exist and is worthy of further consideration and study—particularly, as to its pathophysiology and incidence among patients with psychodynamic complaints The study conducted by Levin should be regarded as a praiseworthy and important contribution to this enigma, but hardly the last word The scepticism professed by *The Lancet* concerning the unsettled existence of euthyroid hypometabolism is looked upon as healthy and challenging, but an obituary is decidedly premature

Worcester,
Mass

MARSHALL GOLDBERG

*** Our annotation was intended as a challenge to those who believe in the existence of this syndrome, and we are delighted that Dr Goldberg has responded He rightly points out that a "double-blind" trial is not ipso facto sacrosanct and is often open to criticism on other grounds Nevertheless, it seems to us that no firm conclusions can be drawn about the effects of therapy in a condition which "often masquerades as a psychoneurosis" (Dr Goldberg's words), unless a double-blind procedure is employed The obvious answer to our criticism would be for Dr Goldberg to repeat Levin's observations, using the dosage and duration of therapy which he considers adequate Until he has done so (and there is no indication in his letter that he has), we feel justified in reserving judgment on his claim that "triiodothyronine is completedly effective in relieving the so-called 'psychoneurotic' complaints in the vast majority of 'hypometabolic' patients" —ED L

CAUSE OF ŒDEMA IN "COR PULMONALE"

SIR,—In their article of May 28, Dr Campbell and Dr Short state that œdema in chronic lung disease is not closely correlated with a raised venous pressure. An absence of the urinary abnormalities of heart-failure (high specific gravity, proteinuria, cells, and casts)[1] is further evidence against attributing the œdema in these cases to myocardial failure *Similarly,* abdominal palpation may fail to show the signs of passive venous

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[1] *Lancet,* Feb 27, 1960, p 480

[2] Lawson, J D *New Engl J Med* 1958, 259, 761

[1] Segall, J J *Lancet,* 1953, i 524

Case no	Sex	Age	Ætiology	Increased jugular venous pressure	Palpable liver	Hepatic tenderness	Ascites	Proteinuria	Œdema
23	F	76	Presumed ischæmic heart-disease auricular fibrillation, left ventricular enlargment, B P 120/70	+	+	0	0	0	+++
25	M	65	Presumed ischæmic heart-disease auricular fibrillation, B P 130/70	+	+	0	0	0	+++
28	F	81	Presumed ischæmic heart-disease sinus rhythm, B P 190/90	+	0	0	0	0	+++
29	M	63	Pulmonary heart-disease due to chronic bronchitis and emphysema sinus rhythm, B.P 160/80	+	+	0	0	0	+++
49	F	50	Pulmonary heart-disease right ventricular enlargement, auricular flutter B P 140/100	++	+	Not recorded	0	0	+++

0=absent +=slight ++=considerable +++=massive

congestion of the liver—namely, tender hepatic enlargement and ascites

The occurrence of preponderant œdema with minimal venous congestion is not entirely limited, however, to cases of anoxic pulmonary heart-disease In an unpublished series of 52 cases of heart-failure, such disproportionate œdema was present in 5 instances, of which 3 could not be regarded as cases of chronic cor pulmonale The salient features of these 5 cases are shown in the accompanying table, recovery from the attacks occurred with conventional treatments

The suggestion of Campbell and Short that hypoventilation and increased work of breathing may be factors in the production of œdema in cor pulmonale could apply also to other dyspnœic patients who develop preponderant œdema, in elderly patients, for example, atrophic emphysema could play a similar role in the genesis of the œdema The importance of increased work of breathing in the production of cardiac œdema has received a therapeutic confirmation in a recent report that tank-respirator treatment alone may cause elimination of œdema in decompensated cor pulmonale [2]

London, N W.2 J J SEGALL

FLUORIDATION

SIR,—Lord Douglas of Barloch (June 4) draws attention to the finding, by the Councils on Drugs and on Foods and Nutrition of the American Medical Association, that there was a statistical difference in the deaths at Bartlett and at Cameron and suggests that it may be that the Ministry of Health "does not consider death to be an important effect"

The original report on Bartlett and Cameron came from the National Institute of Dental Research in 1954 and 1955 and stated that there were no significant differences between the age-adjusted death-rates in the two towns, and the Ministry of Health paper was dated 1955 Using a different, more exact, method of statistical analysis, the Councils quoted above later found that "the odds are approximately 1 in 21 that mere chance determined the difference ($p=0\ 048$)"

This point is only made here to answer Lord Douglas' insinuation that the Ministry may view death callously The real question is whether the difference was in fact due to the fluoride in the Bartlett water, or to some other difference between the two towns, in other words, whether it was an important effect in the context of the Ministry of Health's reference note which deals with fluoridation Here, Lord Douglas omitted the ensuing sentences from the Councils' report "This one comparison, however, must not be given undue weight Roholm's view on general toxicity has just been quoted, his cryolite workers probably had more than twice the fluoride exposure of the Bartlett residents" Roholm states (and here we pass to the preceding page of the Councils' report) "There is nothing to show that working with cryolite reduces the period of life or that cryolite workers acquire macroscopically recognisable organic lesions apart from the bone changes" The Councils' view on Roholm's work, which was published in 1937, was that it "is still the most detailed and reliable on chronic fluoride poisoning"

I could advance further evidence to support the view that the higher death-rate at Bartlett was not due to fluoride, but I am very conscious of the space which has already been occupied by this correspondence Suffice it to say that the board of trustees of the American Medical Association House of Delegates, after study of the Councils' report, reached the opinion that "fluoridation of public water supplies is a safe and practical method of reducing the incidence of dental caries during childhood"

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A J DALZELL-WARD
Medical Director

SEX CHROMATIN IN SOMATIC NUCLEI

SIR,—Reconstructions of Feulgen-stained serially cut human and rodent somatic cell nuclei have made it likely that all the chromatin masses which are seen in nuclei as seemingly free and discrete features are in fact nucleolar associated chromatin [1] In fixed preparations the chromatin covers the nucleoli as one or more caps which when sectioned may appear as unattached chromatin masses As the nuclei are randomly orientated with respect to the direction of the cutting the chromatin masses may seem to be randomly distributed, and the frequency with which a given chromatin mass is observed in a given position is therefore determined by the ratio between the dimensions of the feature and the nucleus

It is stated [2 3] that the female sex chromatin is approximately 1μ "in diameter", located on the inside of the nuclear membrane, and found with a frequency of 60–80% in 5μ-thick sections of female somatic tissue and with a frequency of 5–10% in male nuclei If the sex chromatin is synonymous with the XX-chromosome there can only be one such feature per somatic female cell nucleus If this were so the frequency with which it would be observed in its characteristic locations in sections would be about 40% if the nuclear diameter was as small as 7μ, and the frequency would be even lower if the nucleus were bigger The observed frequency of 60–80% suggests that more than one "sex chromatin" body exists in the female nucleus If this is so, the morphologically recognisable "sex chromatin" might be interpreted as evidence that the nucleus is female and therefore possesses the XX-chromosome, but that this is not synonymous with the "sex chromatin" The findings are, however, fully explicable if we assume a difference on a molecular level in the template-replica system between male and female nuclei And the observed differences in morphology between male and female nuclei of some species may thus indicate secondary sexual characteristics at the level of the nucleus

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[2] Efferöe, P, Kristensen, H S, Lassen, H C A *Brit med J* May 14, 1960, p 1469

[1] Iversen, S *Acta anat* (in the press)
[2] Barr, L. M. *Science*, 1959, 130, 679
[3] Lennox, B *Scot med J* 1956, 1, 97

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SIMON IVERSEN

FLACCID QUADRIPLEGIA FOLLOWING URETERIC TRANSPLANT

SIR,—I was interested to see Dr Angeloni and Dr Scott's article of May 7 on hypokalæmia in a patient with ureteric transplant, in addition to the more commonly recognised hyperchloræmic acidosis We have found this to be a relatively frequent occurrence, in a series of 93 patients over half had hypokalæmia at some time, and in a few cases where full balances were done as much as 600 mEq K was retained before the plasma levels returned to normal These results are to be published later In some cases the K deficiency was not obvious from the plasma figures until the acidosis was corrected, so it may be even more common than is generally realised

Incidentally, this article contained an excellent example of the confusion and inconvenience arising from the use of several systems of weights and measures The patient received 3 litres 0 1% KCl and "mist pot cit *B P C* $^{1}/_{2}$ oz four-hourly", *while his plasma-K was* 1 5 mEq per litre *It requires* considerable manipulation with a slide-rule to discover that he had received over 170 mEq K per day, which after all is the essential information required for treatment, or should be

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ALISON J DINWOODIE

NAMES OF DRUGS

SIR,—I agree with Colonel Walton (June 4) that the nomenclature of drugs would benefit by simplification Practising doctors and their patients must indeed be grateful to the research chemists and the pharmaceutical firms who are providing such a wealth of potent remedies in so many fields, but the names do get baffling May I offer a few suggestions?

1 An effort should be made to find official names which are shorter and less cumbersome Three or four syllables should be the aim, and five should be the maximum Phthalylsulphathiazole, cyanocobalamin, and hydroflumethiazide each have seven

2 There should be less reluctance to adopt a new shorter name for a drug which is proving really useful Why should not phenobarb be the official name instead of the abbreviation for 5-ethyl-5-phenylbarbituric acid? At least it would get rid of the confusion of the synonymous usage of the names phenobarbitone and phenobarbital There can be few other amine derivatives containing cobalt of therapeutic importance, and to rename cyanocobalamin simply as cobalamin could hardly lead to difficulty

3 An agreed series of monosyllabic euphonious prefixes could be established to indicate the various operations performed by chemists on molecules, such as removing or adding methyl, hydroxyl, or amine radicles, much as noradrenaline signifies adrenaline from which a methyl radicle has been removed One or two syllables could then be saved on the "hydroxy", "dehydro", and "demethyl" derivatives of standard preparations

4 Every manufacturer should be required, on all labels, pamphlets, and advertisements, to print the official name of a preparation in letters at least as large and as prominent as those in which the proprietary name is displayed

5 A standard code of pronunciation would be helpful

It is, of course, axiomatic that, before suggestions such as these could be adopted usefully, they would have to be agreed internationally

Bedford General Hospital

R G MILLER

CÆSAREAN SECTION AND HYALINE MEMBRANE

SIR,—According to Snyder[1], whose work is referred to in your leader of March 26, the high incidence of hyaline-membrane disease observed in full-term infants delivered by cæsarean section is related to aspiration of maternal blood This implies that there is an increased danger of "contamination of the lungs by blood-laden amniotic fluid" in deliveries by cæsarean section. An attempt was made to test this suggestion

In a series of 1020 consecutive deliveries, adequate smears of the stomach content[2] were obtained at birth in 960 newborn infants including 65 infants delivered by cæsarean section The smears were examined microscopically for the presence of red blood-cells and classified in three groups according to the number of erythrocytes encountered Since fœtal and immediately postnatal gastric juice is said to show a relative lack of acidity[3], the results are unlikely to be altered by hæmolysis of the swallowed erythrocytes The control group consisted of the 130 normal spontaneous vertex deliveries immediately preceding and following the cæsarean sections The smears were read blindly A comparison of the two groups by the fourfold table method showed no significant difference in the incidence of blood contamination of the stomach content 1 infant of the cæsarean-section group died at the age of nine hours *He was a* 1500-g premature and presented a moderate degree of hyaline-membrane disease There were 4 stillbirths in the control group All 5 dead infants had gastric aspirate rated "none or rare R B C"

Amount of blood in gastric content	Cæsarean sections	Normal deliveries	χ^2	P
None or rare R.B C	50	90	0 003	>0 95
Moderate	9	23	0 79	0 5>P>0 3
Abundant	6	8	0 24	0 7>P>0·5
Total	65	130		

If one admits the reasonable assumption that the gastric content is fairly representative of the amniotic content, then "cæsarean-section babies" are not exposed more frequently than other babies to the aspiration of blood-laden amniotic fluid. Therefore, the increased incidence of hyaline-membrane disease after delivery by cæsarean section seems related to other, more complex events

These results do not rule out the possible role of exogenous material as a subsidiary or contributing factor in the pathogenesis of the membranes There is morphological evidence at hand supporting the exogenous pathogenetic theory, at least in some types of membranes The "vernix" membrane[4], usually found in full-term infants, is made up of vernix caseosa containing squames and cellular debris and takes fat stains The "fibrin" membrane is found within foci of hæmorrhage[5] or blood aspiration It is limited to these areas and tends to be more refractile and eosinophilic than the typical "hyaline" membranes of premature infants It takes ordinary fibrin stains, whereas special techniques are required to demonstrate fibrin in typical "hyaline" membranes[6] The latter type is now considered a result of transudation[7–9] and merely the end stage of a complex process The demonstration of aspirated material within the membrane[10–13] does not contradict the transudation theory The "hyaline" membranes are distributed diffusely throughout all lobes, contain little or no fat, nuclear and cellular debris and show no consistent correlation with the presence of

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1 Snyder, F F *Obstet Gynec* 1959, 14, 267
2 Blanc, W A *Clin Obstet Gynec* 1959, 2 705
3 Ebers, D W, Smith, D I, Gibbs, G E *Pediatrics*, 1956, 18, 800
4 Farber, S, Sweet, L K *Amer J Dis Child* 1931, 42, 1372
5 Landing, B M *Pediatrics*, 1957, 19, 217
6 Craig, J M, Fenton, K., Gitlin, D *ibid* 1958, 22, 847
7 Tessereaux, H *Frankfurt Z Path* 1949, 60, 188
8 Gruenwald, P *J Amer med Ass* 1958, 166, 621
9 *Lancet*, 1958, ii, 945
10 Ahvenainen, A K *Acta pædiat* 1948, suppl 35
11 Blystad, W, Landing, B H, Smith, C A *Pediatrics*, 1951, 8, 5
12 Blanc, W A *Arch Sci* 1951, 156, 388
13 Claireaux, A E *Lancet*, 1953, ii, 749

aspirated material, inflammation, or hæmorrhage They are rarely found in alveoli where "vernix" and "fibrin" membranes are less uncommon In most cases, one sees also amorphous pale-staining albuminous material lying in alveolar ducts and atria Although not found primarily in alveoli as in pulmonary œdema, stricto sensu, this material is similar to œdema fluid. Pulmonary lymphatic vessels are engorged and œdema is present in other tissues [14] These generalised changes are associated with a definite clinical syndrome It is not certain whether the membranes formed by air-bubbles in areas of œdema [5] should be distinguished from hyaline membranes since they may well represent an early stage of the latter

At the present time the "fibrin" membrane is the only one definitely associated with the presence of blood in the bronchial and alveolar spaces On the basis of the cytology of neonatal gastric content and of pulmonary morphology, it appears unlikely that intrapartum aspiration of blood is related to the formation of the typical hyaline membrane

A variety of causes have been attributed to different conditions grouped under the all inclusive term of hyaline-membrane disease If this term is to be retained at all, it seems that an agreement on a nomenclature of neonatal pulmonary membranes would eliminate some apparent divergences of opinion This might, in turn, accelerate the shift of interest of morbid anatomists from the membranes, an end result, to the underlying causes of the "respiratory distress syndrome" and its humoral [15] and circulatory [16–18] aspects

Department of Pathology, College of Physicians and Surgeons, Columbia University and Babies Hospital and Sloane Hospital, New York

WILLIAM A BLANC
PAUL P GWYN, Jr

SIR,—In your leading article one is impressed with the importance of blood constituents in the formation of hyaline membrane It is a little surprising then that there is no reference whatever to the original work which showed that the membrane (both natural and experimental) contains hæmoglobin in abundance [19,20] May I draw attention to the fact that our work was also the first to record the hyperkalæmia associated with the condition ? [21]

Sudbury General Hospital,
Sudbury, Ontario

M J LYNCH

CONFIRMATORY MEDICAL CERTIFICATE BEFORE CREMATION

SIR,—I should like to draw attention to question 3 of the confirmatory medical certificate required before a cremation The question is "Have you made a postmortem examination ?" Now in this hospital (as in many others) necropsies on my patients are performed by the morbid anatomist, who is expert at the job, and not by myself, it follows I have to reply "No" But there is no other question on the certificate asking about postmortems, so this negative answer might well be taken to mean that necropsy was not carried out at all Surely it is more important for the medical referee, who checks the certificate, to know that a postmortem examination was in fact carried out, than to know who did it?

I understand these questions are statutory, so I put this difficulty to the Home Office, who replied " there would appear to be advantage in providing this information in answer to Question 3 even if the information is additional to that required by the actual wording of the question " But would it not be better to alter the wording of the question, so as specifically to ask for this information ?

Whipps Cross Hospital,
London, E 11

E HINDEN

AN UNUSUAL FORM OF OSTEODYSTROPHY

SIR,—An account of an unusual family with some form of osteodystrophy is given in your issue of June 4 by Dr Stuart Barber, unfortunately his report is vitiated by the poor quality of the radiographic reproductions As the classification of these cases depends to so great an extent on radiographic interpretation the value of such reports to students of rare dystrophies and dysplasias of bone is largely lost Because they are such rarities, atypical cases such as Dr Stuart Barber reports are of great interest, and their eventual recognition as clinical entities depends mainly on the correlation of isolated case-reports Not every journal will extend the hospitality of its columns to such accounts which at present are of scientific rather than practical value, when they do so it is all the more important that radiographs are reproduced with the highest fidelity Although they are admittedly more expensive, may I make a plea for the more generous use of special plates on future occasions ?

Cambridge

T J FAIRBANK

MATERNAL INFLUENZA AND CONGENITAL DEFORMITIES

SIR,—Before I deal with the points raised by Dr Trimble (May 28) I should like to make it clear that my part in the study on maternal influenza and congenital deformities was little more active or laudable than that played by a spectator on the 2*s* (shortly to be 2*s* 6*d*) terraces in the victory of his favourite team on a Saturday afternoon The credit for conception and execution of this interesting and important research lies with Dr Coffey and Professor Jessop alone

I am sure that the authors would be the first to agree that the Dublin study may have methodological faults, but I am not sure that selecting patients for inclusion in the case group on the basis of self-diagnosis is, as Dr Trimble (Jan 9) suggests, a fault of any moment

Had it proved possible to establish the diagnosis serologically the distribution of patients between case and control groups might have been changed in one of two ways First, it might have been found that some of the women replying in the affirmative to the question "Have you had influenza during this pregnancy ?" had in fact suffered from something else, and if this something else was a teratogenic disease the validity of the results would certainly have been in doubt The contemporary work of Meenan [1], however, suggests that influenza virus A was the only infective agent active to a significant degree at the time Second, the control group might have been shown to contain women who had been infected with the virus, and on the evidence of Wilson [2] and Walker [3] and their collaborators it is highly likely that the latter would have proved to be the case Yet despite this probable impurity, the mothers in the control group bore almost the same proportion of malformed children as those in an earlier Dublin survey [4] which had been conducted when there was no epidemic of influenza Thus, the Dublin study showed that those mothers in the city who had influenza and remembered it (and were presumably therefore really incapacitated) bore a greater proportion of malformed babies than those who were well throughout their pregnancy, or those who were infected by the influenza virus and did not remember it (and presumably remained more or less symptom-free) When these facts are taken together, and it is borne in mind that the mothers made their " self-diagnosis " *before* they knew the outcome of their pregnancy, I do not see how Dr Trimble can reasonably question the implications of the Dublin study (Jan 9)—always provided that he does not extrapolate from women who felt ill from influenza in Ireland to women in more prosperous communities who had a subclinical infection

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[14] Anderson, D H *in* James L. S (ref 18)
[15] Usher, R *Pediatrics*, 1959, 24 562
[16] Nodot, A Thesis, Paris, 1958
[17] Shanklin, D R *A.M.A Arch Path* 1959, 68, 49
[18] James, L S *Pediatrics*, 1959, 24 1069
[19] Lynch M J G *J Pediat* 1955, 47, 275
[20] Lynch, M J G *ibid* 1956, 48, 165
[21] Lynch M. J G, Mellor, L D, Badgery, A *ibid* p 602

[1] Meenan P N Personal communication to Coffey and Jessop (*Lancet*, 1959, ii 935)
[2] Wilson, M G Heins H L, Imagawa, D T, Adams, J M *J Amer med Ass* 1959, 171 638
[3] Walker, W M, McKee, A P *Obstet Gynec* 1959 13, 394
[4] Coffey, V P, Jessop, W J E. *Irish J med Sci* 1955, 6, 30

Coffey and Jessop argue in their discussion that such teratogenic effect as may be associated with influenza is unlikely to be due to direct infection of the fœtus by the virus, and a comparison between their findings and those of Walker and Wilson lends support to this view In my previous letter (April 30) I referred to some of the evidence which shows that the women attending the three Dublin maternity hospitals are an underprivileged group, and it may well be that in the case of influenza it is not the infecting agent itself, but the systemic disturbance of a severe infection in a woman who is already sorely taxed in supporting her pregnancy, which is the factor that damages the fœtus

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Tropical Medicine, London, W C 1

ROY M ACHESON

TREATMENT OF SALICYLATE POISONING

SIR,—I am grateful to Dr Macdougall and Dr Cameron (May 28) for their opinions concerning " the efficacy of curarisation in reducing hyperpyrexia caused by salicylate "

In my letter of May 14 I was not suggesting that curare itself lowers the pyrexia which frequently accompanies salicylate poisoning However, when respiratory obstruction occurs, particularly when the patient is hyperventilating and in a state of tetany, the extra work invoked in breathing against resistance frequently aggravates the pyrexia In the case recorded by Freier et al [1] the secretions were removed and the relaxed tongue bypassed by means of curarisation, intubation, and controlled ventilation This combination of factors, and not the curare alone, soon resulted in the temperature falling from 101° to 99 4°F

I agree with their suggestions that the drugs used in the induction of hypothermia may have a place in reducing pyrexia They would be most useful in those cases where the pyrexia is so pronounced as to endanger the life of the patient I feel, however, that if the patient is curarised then this aim may be attempted by the application of ice bags In this way the side-effects of other drugs would not complicate the picture

Southmead General Hospital,
Bristol

FRANK WILSON

ANHIDROSIS AND HEATSTROKE

SIR,—In his letter last week Dr Ladell discussed the sudden cessation of sweating during exposure to dry heat

In my view this is due to fatigue or degeneration of the nervous supply of the sweat-glands This is very common in the ageing and is found in all cases of disseminated sclerosis, nervous degenerations, and asthma, and in advanced liver and kidney diseases Under wet heat with refrigerant fluids to maintain thermal balance in the cerebral circulation [2] the sweat-glands do not fatigue and can be kept continuously under secretion for as long as thirty days with skin temperatures at between 96°F and 100°F

In my view the sweat-glands are activated by two mechanisms By one, under dry heat evaporation acts as a refrigerator to maintain thermal balance This is under nervous control as are also gustatory and cold sweats due to nervous tension The other mechanism under wet heat at skin temperatures from 90°F to 115°F, acts directly on the sweat-glands and continues to act on the glands even if their nerve-supply is fatigued and unresponsive to nervous stimuli This second method of activation of the sweat-glands is relevant to the treatment of heatstroke, where wet heat to reactivate the sweat-glands plus refrigeration of the cerebral blood-supply by cooling the head must give quick and direct relief

Tunbridge Wells

E F ST J LYBURN

IMMEDIATE TREATMENT OF CEREBRAL INFARCTION

SIR,—Following the paper by Dr. Barham Carter (Feb 13) may I call attention to the treatment of the acute stage of cerebrovascular accident (" incipient apoplexy ") by intravenous administration of aminophylline or of an analogous theophylline compound

After twelve years of clinical trial I suggested [1, 2] this treatment in 1948–49, and elaborated upon it in later publications [3–10] In an important percentage of cases (35–80%) the slow intravenous administration of aminophylline abolishes within a few minutes the initial manifestations of cerebrovascular accident (hemiplegia and/or coma) *provided the injection is given in the first hour after onset of symptoms* Soon after our first report confirmation came from several authors [11–18] and others

Return of consciousness and/or disappearance of paralysis is sometimes so rapid that the experience has been described as "startling" or "dramatic" On the other hand, unlike similar attacks in hypertensive encephalopathy, general paralysis, or multiple sclerosis, the sudden restitution of cerebral function is uncommon in the natural history of cerebrovascular accident of arteriosclerotic origin

Which conditions in the various forms of cerebrovascular accident are susceptible to be influenced by aminophylline? Vasomotor action and the relief of cerebrovascular spasm have been proposed as the mechanism involved But it is now well established that, in contradistinction to the views prevailing two decades ago, aminophylline has in fact a vasoconstrictor action on the cerebral circulation, this, however, is true only for the *total* cerebral flow as estimated by the Kety procedure Anyhow, for these reasons the clinical effect of aminophylline in cerebrovascular disease can hardly be related to vasomotor effects The very fact, however, that this theoretical concept was initially linked with this treatment may have fostered in England and the U S A a scepticism which prevented a clinical trial

Another mechanism of action was first suggested by Jarisch [19] Aminophylline increases the permeability of the blood-brain barrier and blood-eye barrier and greatly reduces intrathecal pressure The increased permeability may enhance the reduction of œdema and the washing out of cytotoxic metabolites, both due to the existing ischæmia The favourable effect of reduced intrathecal pressure under these conditions is obvious

Reduction of cerebral metabolism [20] and the familiar stimulating and awakening action of aminophylline on central-nervous-system function have been proposed by others as the underlying mechanism of its effect in cerebrovascular accident [21]

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[1] Freier, S , Neal, B W , Nisbet, H I A , Rees, G J , Wilson, F *Brit med J* 1957, i, 1333

[2] *J Physiol* 1956, 134, 207

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1 Mainzer, F *Therap Umschau (Berne)*, 1948, 5, no 2
2 Mainzer, F *Schweiz med Wschr* 1949, 79, 108
3 Mainzer, F *Med Klin* 1951, 46, 938
4 Mainzer, F *Münch med Wschr* 1952, 94, 1724
5 Mainzer, F *Sem Hôp , Paris*, 1953, 29, 163
6 Mainzer, F *Verhdlg Dtsch Ges Kreislaufforschg* 1953, 19, 246
7 Mainzer, F *Nervenarzt*, 1953, 24, 278
8 Mainzer, F *Acta med scand* 1953, 146, 362
9 Mainzer, F *Dtsch med Wschr* 1954, 79, 37
10 Mainzer, F *Alexandr med J* 1956, 2, 13
11 Schimert, G *Med Klin* 1950, 45, 1038
12 Schimert, G *Dtsch med Wschr* 1951, 76, 1176
13 Schlegel, A *Berl Aerztebl* 1951, 64, 17
14 Schlegel, A *Therap Gegenwart* 1952, 91, 212
15 Schmidt-Voigt, H -J *Med Welt* 1952, 20, 1090
16 Dimitrijevic, D T Personal communication, 1952
17 Stockert, v F G *Nauheimer Fortbildungslehrg* 1953, 14, 44
18 Novotny, K *Wien klin Wschr* 1953, 65, 1017
19 Jarisch, A Personal communication, 1952
20 Müller, R , Schild, W *Münch med Wschr* 1955, 97, 1060
21 Perlick, E *ibid* 1957, 99, 877

Whatever the mechanism, ten years' experience of many workers in Europe fully justifies a trial of intravenous aminophylline in incipient cerebrovascular accident.

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FR MAINZER.

RENAL HYPERTENSION

SIR,—Your leader of May 7 has unique significance for the obstetrician interested in the ætiology of toxæmia. In the first instance it has shown that evidence derived from the experimental animal has an actual counterpart in human disease, and, secondly, that renal ischæmia can account for a reduced urinary volume and an abnormally low concentration of sodium in the urine from the experimental kidney.

The animal researches of Mueller et al.[1] had already demonstrated this, and Howard et al.[2] have used these urinary changes as a means of clinical identification of the ischæmic kidney involved in renal hypertension.

Mueller divided his experiment into certain stages. In the earlier, *light* constriction of one renal artery of a dog caused in that kidney a marked decrease of sodium and water excretion without detectable falls in glomerular filtration-rate or renal plasma-flow, while in the later, *heavy* constriction produced a further fall in sodium and water output *and* a decrease in glomerular filtration-rate and renal plasma-flow. Howard's clinical and biochemical findings have demonstrated a fall in sodium and water output, while Shackman and Graber,[3] in their studies on divided renal clearance studies in hypertension, confirmed the decrease in glomerular filtration-rate and plasma-flow. Unilateral renal ischæmia has been shown, therefore, both in animals and in man, to cause hypertension, to lower the glomerular filtration-rate and renal plasma-flow, and to diminish the excretion of salt and water, thereby providing a potential cause of œdema and hypertension.

Fajers,[4] by imposing short periods of unilateral renal ischæmia in animals, caused proteinuric substances to appear in Bowman's capsule, thus in turn supplying an explanation of albuminuria.

Byrom,[5] in his very important researches in rats, has further shown that unilateral renal ischæmia, effected by the Goldblatt clamp, produces both hypertension and hypertensive encephalopathy as a result of cerebral vascular spasm—conditions that quickly abate when the clamp is released. He also found that when normal saline was substituted for drinking-water in these animals sudden generalised œdema sometimes developed, the onset of the cerebral attack being accelerated by this procedure.

The experimental production of salt and water retention, hypertension, albuminuria, and fits in animals by renal ischæmia (albeit unilateral) must strikingly compare with the clinical signs of pre-eclampsia/eclampsia. The uterorenal reflex can visually provoke bilateral renal ischæmia,[6] and it has been shown to reduce the renal plasma-flow by 25%[7]—both in animals. Clinically, conditions causing the myometrium to resist stretch have been shown to underlie the toxæmic state[6] and much evidence has accumulated that there is a reduction in renal hæmodynamic values and cerebral circulation in severe pre-eclampsia. Further, the exhibition of renal vasodilator drugs—e.g., apresoline—have proved of infinite value in the control of the pre-eclamptic state, thus emphasising the underlying renal ischæmia.

That resistance of the uterus to stretch has been clinically recognised in the ætiology is evident in the treatment practised by Krishna Menon[8] who has stressed the immense and unmistakable value of rupture of the membranes in the urgent treatment of toxæmia. One recent and very important finding is that of Reynolds[9] which helps strongly to support my ætiological thesis. These authors have shown that *the tension in the uterus mounts when the uteroplacental circulation is obstructed* either by active or passive engorgement of the placenta. Hereby the infarcted large or hydatidiform placenta can be included in the ætiological thesis of resistance to uterine stretch.

It becomes evident on all sides that impartial assessment of worthwhile data confirms the correctness of the uterorenal ætiology of toxæmia.

Worthing

JOHN SOPHIAN

PROGNOSIS FOR ALCOHOLICS

SIR,—Allow me to add some information to your note (May 7) about my article[10] which Dr Glatt commented on (June 4). Abuse before the age of 21 correlated −0·25 with the follow-up result, no abuse before the age of 30 correlated +0·18, age over 40 in itself +0·11, more than five arrests for drunkenness −0·25. An important feature of the treatment plan was the appointment in each case of a "trustee" (wife, mother, employer, &c.), who dispensed the tablets and reported weekly to the supervisor.

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Gothenburg, Sweden.

C.-G. BERGLIN

A NEW DIAGNOSTIC TEST IN AMYLOIDOSIS

SIR,—May I comment on the preliminary communication by Dr Jarnum in your issue of May 7. He is undoubtedly correct in assuming that Evans-blue is taken up by amyloid tissue, but this observation is certainly not original and was mentioned by Unger et al.[11] as far back as 1947. Furthermore, these authors noted that at necropsy much of the Evans-blue had been absorbed by any amyloid tissue present in the body.

Before any of the tests described by Dr Jarnum start being widely used, I would like to draw attention to some not too obvious fallacies. In the first procedure he describes, it is recommended that blood samples are taken at 4 and 15 minutes after the injection of a known quantity of Evans-blue. The dye content of each sample is then compared, and if the second specimen contains 80% or less dye than the 4-minutes specimen, Dr Jarnum feels that amyloidosis is probable. It is assumed in this procedure, first, that mixing of the dye is complete in 4 minutes, and, second, that no significant amount of dye is absorbed in this period. Neither of these assumptions is correct.[11,12] It can be shown very simply that mixing is incomplete till 8 to 10 minutes after injection by giving intravenously a small dose of human serum-albumin tagged with ^{131}I (I.H.S.A.) and then taking blood samples at 2-minute intervals for the next 14–16 minutes. Each sample is counted and it is found that constant counts occur only after 8–10 minutes. If congestive failure is present, mixing may be delayed for 20–25 minutes after injection.

The second procedure assumes that the binding capacity of serum for Evans-blue is always the same in the absence of amyloidosis. In practice the binding capacity of serum for vital dyes and hence the rate of loss of dye from serum probably depends not only on the level of serum-albumin but on other protein constituents of the serum.[13] It would seem that Evans-blue is a useful agent for measuring plasma-volumes only when there is no dysproteinæmia in the subject being investigated.

University of Maryland
School of Medicine, Baltimore.

W. K. C. MORGAN

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[2] Howard, J. E., Berthrong, M., Gould, M., Yendt, E. R. *Bull. Johns Hopk. Hosp.* 1954, 94, 51.

[3] Shackman, R., Graber, I. G. *Brit. med. J.* 1956, i, 1321.

[4] Fajers, C. M. *Acta path. microbiol. scand.* 1955, suppl. 106.

[5] Byrom, F. B. *Lancet*, 1954, ii, 201.

[6] Sophian, J. Toxæmias of Pregnancy, London, 1953. See also *Excerpta Med.* 1958, sec. x, 11.

[7] McGaughey, H. S., Weller, H., Anslow, W. P. *Amer. J. Obstet. Gynec.* 1956, 72, 559.

[8] Krishna Menon. Lecture at University College Hospital, London, May 31, 1960.

[9] Reynolds, S. R. M., Bieniarz, J. Z. J. (in the press). Quoted by Ramsey, E. M. *Amer. J. Obstet. Gynec.* 1959, 77, 1016.

[10] *Svenska Läkartidn.* March 11, 1960, p. 831.

[11] Unger, P. N., et al. *J. clin. Invest.* 1947, 27, 111.

[12] Morgan, W. K. C., [illegible], J. E. *Amer. J. med. Sci.* 1960, 239, 61.

[13] Larsen, B. *Ann. rheum. Dis.* 1955, 13, 211.

"SPIRITUAL HEALERS" IN HOSPITAL

SIR,—Mr Harry Edwards (June 11) assumes that Dr Cotton Cornwall has presented the strongest case against the new practice of allowing "spiritual healers" to attend the sick in hospitals I would like to record an experience of mine in this connection

I was invited to attend a demonstration of spiritual healing given by Mr Edwards in the St Andrew's Hall, Norwich, on Nov 12, 1949

He began by saying that any healing that they might see would not take place through any physical skill of his or his helpers A number of patients were brought on to the platform, one of them being a little girl with poliomyelitis affecting one leg, who happened to be a patient of mine She was lifted on to the platform and into a chair and was wearing a short iron, to support a flail foot, which had been ordered by me The healer approached the child and ordered removal of the iron and then took the child by the hand and said "get up and walk", which she did to the astonishment of everybody Of course, they did not know that the child could walk like that beforehand, but I did There were even cries of "it's a miracle" I saw the same child the next week at my clinic at the Children's Hospital, there was no change whatever in her condition and fortunately the mother had replaced the short iron

There were other cases "healed" at the same time I remember one of them quite well—a man with a stiff shoulder, which was quite vigorously manipulated in direct contrast to the opening words of the healer The patients were subjected to suggestive treatment and were encouraged to do their best in front of a large audience, and there was also a certain amount of handling and manipulations—all well-recognised methods of treatment, but not spiritual healing

I would like to say that I am a firm believer in cooperation between medicine and the Church But these experiences of mine put "spiritual healing" as demonstrated in Norwich in November, 1949, at quite a different level If benighted patients want this form of treatment let them go and have it at the spiritual healer's home or centre, but not in the recognised hospitals of this country

Norwich. G K McKEE

FATTY FOODS AND OBESITY

SIR,—In their letter of May 28, Professor Kekwick and Mr Pawan repeat their claim that a decrease in body constituents other than water (i e, fat) is involved in the weight-loss produced over a short period by a fatty diet, in other words, that such a diet brings about an increased tissue catabolism If Kekwick and Pawan were right in this contention, it should be easy to demonstrate, during the high-fat period, the increase in energy expenditure which must necessarily accompany the accelerated combustion of fat However, present evidence, including our experiment, is against any significant increase in metabolic-rate on a high-fat regimen, if more fat is burnt on the unaltered oxygen consumption recorded by us, it has to be at the expense of other fuel, probably carbohydrate, and this would even indicate a reduced energy utilisation, considering that 1 litre of oxygen used for burning fat yields fewer calories than 1 litre used for combustion of carbohydrate (about 4 7 and 5 0 kCal, respectively)

Kekwick and Pawan's demonstration of a fat-mobilising factor released on a high-fat regimen is most interesting, but does not exempt us from observing the law of constant energy the fact that more fat is mobilised might be expected to result in hyperlipæmia, but it does not per se indicate that more fat is burnt

The increase in insensible water loss which Kekwick and Pawan have found in patients on a fatty diet is no reliable indicator of a corresponding increase of the metabolic-rate, thus Passmore, Strong, and Ritchie [1] found that evaporative water-loss varied considerably although calorie expenditure and diet remained unaltered

Nor should we be too much impressed by the fact, also referred to by Kekwick and Pawan, that high-fat feeding inhibits the in-vitro lipogenesis in adipose tissue from rats [2]—in view of the observation that rats do actually grow fat on high-fat diets [3]

Until the disappearance of fat is properly accounted for, we feel justified in "falling back on to the old argument" that a change in total body-water is the major reason for the changes occurring in body-weight when shifting between equicaloric diets rich in either fat or carbohydrate In our support we may cite Benedict and Milner [4] who demonstrated a large negative water balance on a high-fat diet and, conversely, a positive balance on a high-carbohydrate diet Also Passmore et al [1] found a positive water balance in two persons receiving 1000 calories with 90% carbohydrate

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E S OLESEN
F QUAADE

HEPATITIS AFTER INOCULATIONS

SIR,—Twenty years ago the late Sir Alexander Fleming used to demonstrate a method of sterilising a single syringe and needle for use during mass inoculations Medicinal paraffin heated over a flame to about 150 C was sucked in and out of the syringe, with the needle in situ, between each injection I have never used this simple method myself, but I am surprised that no-one from St Mary's has written to you about it

London, N W 1 JOHN BRAY

LATEX AGGLUTINATION REACTION IN NON-RHEUMATIC DISEASES

SIR,—In your annotation of March 26 and in Dr Morgan's letter of April 9, the topic of latex agglutination reaction in non-rheumatic diseases was discussed You correctly underscored Dresner's findings [5] as emphasising a basic difference between the factors responsible for agglutination of globulin-coated latex particles and the agglutination of erythrocytes sensitised with "amboceptor"

Recent studies of Epstein et al, [6] Lospalluto and Ziff, [7] and Franklin [8] have clearly demonstrated that there are at least two rheumatoid factors One of these reacts with rabbit gamma-globulin, the other with human gamma-globulin. Those observations should be taken into consideration when interpreting discrepancies between latex fixation tests and "amboceptor"—sensitised erythrocyte procedures The latex (polystryene) particles are coated with human gamma globulin, whereas the red cells used for the Rose-Waaler D.A T were coated with rabbit antibody gamma-globulin (amboceptor)

In our own laboratory [9] we have found that alligator erythrocytes lend themselves to detection of rheumatoid factor(s) by direct or inhibition hæmagglutination procedures We have observed that 6 of 44 subjects with liver disease due to carcinomatosis or cirrhosis were positive by alligator hæmagglutination By slide latex fixation, 7 were positive Whereas

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1 Passmore, R, Strong, J A, Ritchie, F J *Brit J Nutr* 1959, 13, 17
2 Măsek, J, Fábry, P *Experientia, Basle*, 1959, 15, 444
3 Hausberger, F X, Milstein, S W *J biol Chem* 1955, 214, 483
4 Benedict, F G, Milner, R. D Experiments on the metabolism of matter and energy in the human body, 1903–1904 Bull 175 U S Department of Agriculture Office of Experiment Stations, 1907
5 Dresner, E, Trombly, P, O'Brien, G F *New Engl J Med* 1959, 261, 981
6 Epstein, W, Johnson, A M, Rogan, C *Proc Soc exp Biol Med* 1956, 91, 235
7 Lospalluto, J, Ziff, M *J exp Med* 1959, 110, 169
8 Franklin, E G *Arth Rheum* 1960, 3, 16
9 Cohen, E, Neter, E, Mink, I, Norcross, B M *Arch Inter-Am Rheum* 1959, 2, 75

cold precipitates and euglobulin fractions of serum of rheumatoid arthritis patients showed agglutinating activity, the precipitates and globulin fractions of sera of patients with non-rheumatoid diseases were often negative, although the whole sera themselves, were actively positive.[10] Sera of subjects with syphilis or of healthy blood-donors have been consistently negative. However, Bloomfield[11] has reported positive latex fixation by sera of patients with syphilis By concurrent use of hæmagglutination, latex fixation and serum fractionation, the agglutination reactions of some non-rheumatoid sera were distinguishable from those of rheumatoid sera

E COHEN
K. SHIMAOKA
P HERMES

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SKELETON IN THE LINEN CUPBOARD

SIR,—The role of blankets in cross-infection is well established, and there has been considerable research into techniques designed to reduce their bacterial content. Unfortunately little thought has been devoted to an equally relevant problem—namely, the maintenance of bacteriological cleanliness in the period between laundering and subsequent use. The importance of this latter factor was realised after a study on bed-linen and blankets carried out after an outbreak of surgical sepsis in which blankets were implicated

It was established that blankets could be rendered relatively and adequately sterile by the method of Blowers and Wallace.[12] It was also found that significant reinfection was occurring during transport and storage.

The procedure then in use was to return freshly laundered bedding to the wards in canvas bags These bags were also used to convey used bedding from the wards to the laundry, but they were washed before being used for clean bedding In the wards the linen and blankets were stored, uncovered, on bare shelves in the linen cupboards. It was noted that no attempt was made to store the bedding in a last-in last-out rotation. It was also customary to store in the cupboard, alongside the freshly laundered material, blankets which had short use in the wards

As a result the linen cupboard contained an assortment of bacteriologically clean and dirty bedding, and tests showed that any blankets not used immediately after laundering soon acquired a heavy bacterial content.

To reduce the hazard of contamination of the blankets during transit and storage a trial was made of packing the blankets in groups of four in a strong polyethylene bag immediately after washing From a bacteriological standpoint this was extremely satisfactory No change in the low or absent bacterial count could be found after prolonged storage or removal of two or three blankets from the bag Economically, however, the method proved disappointing The cost of each polyethylene bag was 5s and there was, for a variety of reasons, a very high wastage during use.

To overcome this difficulty a trial was made using 'Cellophane' sheet instead of the polyethylene bags This proved economically and bacteriologically satisfactory, but due to careless handling during transit the majority of packs arrived in the wards with the cellophane torn. This problem was finally overcome by packing the cellophane-wrapped blankets, three per pack, in a strong fibre case. This method of transport has proved very satisfactory and few if any, tears have arisen since it was introduced. On arrival in the ward the cellophane packs are stored in the linen cupboards care being taken not to damage the cellophane. Tests have shown that the wrapped blankets have remained bacteriologically clean over periods as long as 12 weeks

In order to prevent any ward organisms being introduced into the linen cupboard a complete ban has been placed on the use of the cupboard for storing bedding from the ward. This one-way traffic, laundry/linen cupboard/ward, has been combined with an overhaul of bedding hygiene.

Every patient on admission is put in a bed which is made up with freshly laundered bedding, and under no circumstances are any blankets to be put on an adjacent bed, even though it is unoccupied.

After discharge of a patient both blankets and linen are to be returned to the laundry for washing

If a blanket is required for a patient during transport to another department a freshly laundered one is used. If it is frequently required then it is stored in the patient's locker and must not be put back in the linen cupboard.

Unoccupied beds, as far as possible, are not made up until shortly before a patient's admission, though one or two can be kept ready for emergencies Infected cases must obviously have frequent changes of all bedding All bedding is stored on a last-in last-out basis

It is obvious that if measures are to be taken to produce bacteriologically satisfactory bedding then subsequent handling must be such as not to prejudice the efforts involved.

Cotton and linen goods are boiled during washing and have a greater turnover They have not been found to acquire any resident bacterial flora during storage and are therefore still delivered in canvas bags Blankets, however, do appear to acquire bacteria with greater ease, and the method of cellophane-pack/fibre-bag delivery has proved very satisfactory over the past eighteen months The extra cost is insignificant in comparison with the total work undertaken

In spite of the more frequent washing that blankets now receive the number of new blankets required has not shown any increase.

These rules adopted for linen-cupboard and bedding hygiene are all simple and obvious, and no cases of cross-infection have occurred since their introduction The overall rate of sepsis is appreciably less, infected wounds have shown an increase in the speed of healing, and one noticeable result has been a higher percentage take of skin grafts

It is suggested that the ward linen cupboard is worthy of a great deal more attention from the hospital medical staff than is normally given to it. At the same time the system of delivery of bedding and its subsequent handling in wards must be considered, for we have little doubt that the majority of linen cupboards will be found to contain a very small but highly ubiquitous skeleton.

I McGILVRAY
M H. HALL.

Whiston Hospital,
Prescot, Lancs.

SNAKEBITE

SIR,—The word "envenomation," questioned by Dr. Penman (April 2), although omitted by *The Shorter Oxford English Dictionary* is to be found in *Webster's New International Dictionary of the English Language*[1] (p 855) as follows

(c) "Envenom. 1 To poison as by a venomous bite. Envenomation, n."

"Envenomation" is more specific than "poisoning" when venom is the noxious agent. Since the mildly poisonous *Vipera berus* is the only venom-bearing snake to be found in the British Isles and according to the records of the past 70 years, fatalities from the bite have been extremely rare, it is understandable that the word "envenomation" should have found little use. On the other hand, many highly dangerous species are indigenous to the United States; hence the need of a more specific term than "poisoning."

ELEANOR E BUCKLEY

Wyeth Laboratories,
Philadelphia.

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[10] Cohen, E., Shimaoka, K., Hermes, P *Proc. N.Y. Acad.* [illegible] *Lab.* 1960 (in the press)

[11] Bloomfield, N *J Lab clin. Med* 1960 55, 73

[12] Blowers, R., Wallace, K. R. *Lancet*, 1955, i, 1250

[1] 2nd ed. Springfield, Mass., 19[illegible]

Obituary

HENRY LETHEBY TIDY

K B E, M A, D M Oxon, LL D Belf, F R.C P

Sir Henry Tidy's work as a physician was centred on St Thomas's Hospital and Harley Street, but through his writings, his travels, and his service with the Army he was known and admired by many colleagues outside London and outside this country He died, as we announced last week, on June 3 at the age of 82

Elliott & Fry

He was the only son of Charles Meymott Tidy, who for many years held the chair of chemistry, medical jurisprudence, and public health at the London Hospital, and nearly a century later he used to recall his father's comments on the consultants of the 'seventies and 'eighties He was educated at Winchester, New College, Oxford, and the London Hospital He qualified in 1906 and held resident appointments and a registrarship at the London Hospital before spending some time abroad in the clinics of Freiburg and Berlin On his return he set up in consultant practice in Harley Street His first appointments were at Poplar Hospital and the Royal Northern Hospital, but in due course he was elected to the staff of St Thomas's Hospital, and for many years he was also dean of the medical school

Tidy's wide clinical experience, exhaustive reading, and talent for lucid and orderly exposition were clearly seen in his *Synopsis of Medicine*, which first appeared in 1920 Its success was confirmed in subsequent editions, and the tenth was reached in 1954 He was also for many years one of the editors of the *Medical Annual* His own research was based on clinical percipience reinforced by laboratory investigation—he was a fellow of the Chemical Society, and his early posts included that of clinical pathologist at The London His first papers dealt with gastric contents and leukæmia, and in 1919 he investigated an epidemic due to *B aertrycke* for the then Medical Research Committee But he will perhaps be chiefly remembered for his studies on glandular fever, which in the early 'twenties was prevalent in this country Thanks to this experience he was quick to draw attention to the epidemic which broke out in 1930 His Lumleian lectures to the Royal College of Physicians in 1934 were a valuable and exhaustive review of this protean disease

Tidy also served the college in many offices besides that of Lumleian lecturer He had been elected to the fellowship in 1919, and he was successively elected examiner, councillor, censor, representative on the General Medical Council, and registrar Other medical bodies in which he took a prominent part included the Royal Society of Medicine, the Association of Physicians of Great Britain, and the British Society of Gastroenterology, over all of which he at one time presided

He also had a long association with the Army Medical Services During the 1914–18 war he had served as a major in the R A.M C, and he was honorary consultant physician to the Army at the Queen Alexandra Military Hospital, Millbank, for some years before the late war In 1939 he accepted the appointment of consulting physician to the Army at the War Office, and of this strenuous part of his career A G B writes

"With his previous knowledge of military medical requirements Tidy was well qualified to advise the director-general, and all who worked with him found his quiet manner in dealing with difficult problems helpful not only to the specialist medical officer but also to the administrative medical staff He took a special interest in the regimental medical officers and when visiting commands always made a point of seeing them and helping them with their problems "

Tidy reached the rank of major-general and was knighted in 1943 He also received awards from the Governments of the United States, Holland, Belgium, and Czechoslovakia

After his retirement from St Thomas's his interests were widened by his appointment as a visiting professor to the University of Cairo From 1946 to 1951 he spent each winter in Egypt, and of these visits W R B writes

"Harry Tidy's outstanding qualities—commonsense, thoroughness, perseverance, and kindness—though not, perhaps, exceptional ones—made him in his way an exceptional man The capacity to extract the essentials of a subject or situation was the basis alike of his best-selling textbook, and his clinical acumen, and his commonsense and friendliness soon established him as a British institution in Egypt—a kind of British pasha in the days when there were still pashas From Christmas to Easter he regularly taught in the Medical School, and practised in Cairo to the great advantage of Egyptian medicine, and Anglo-Egyptian understanding was fostered by the lasting friendships he and Lady Tidy formed with the leading Egyptian doctors and their families Their zest for new scenes was unabated by age and they recently sailed round the world, paid a visit to the Persian Gulf, and were hoping to go to British Guiana "

From 1929, when he was appointed a visitor, Tidy had shared in the work of King Edward's Hospital Fund. He served on the hospital economy committee in the 'thirties, and was appointed to the general council in 1936 But from the end of the war to within a few months of his death he gave it a great part of his time He served on the distribution and management committees, the committee of the Hospital Administrative Staff College, and on all his firm character and good sense gave weight to his opinions But perhaps his chief interest lay in the convalescent homes committee which he started from nothing in 1946 R E P recalls

"When Sir Henry started he knew little or nothing about convalescent homes—or so he said These were not famous places like St Thomas's or The London where his roots lay, but he set about learning about them with diligence and by constant visiting His wise and kindly approach to the problems of those small homes won him many friends so that his visits were happily awaited—much more for the pleasure of meeting him than for the possible financial benefits Nevertheless, the financial side was important and he could act with speed. One July day he found a home's milk supply hidden under the front-door step to keep it cool At once he said '*Go and buy a refrigerator today and I will get a grant for it later*' He had a warm place in his heart for those who worked for the good of others without thought of profit or reward and many a chairman or matron of a modest home will regret the loss of a friend "

R C J adds this personal tribute

"Henry Tidy, notwithstanding his very remarkable professional achievements was a modest, rather retiring type of man He never threw his weight about When we were at Oxford together he showed considerable athletic skill and was no mean performer in running and boxing He was president of the St Thomas's Athletic Club in which he always took great interest For the greater part of his life he devoted himself to his work and except for occasional golf and fishing allowed himself little in the way of recreation He possessed a very sound judgment, his wise counsel was much valued by the many committees on which he served He was a true friend and a loyal colleague Tidy had a quiet sense of humour and this, with his kindly and gentle manner, gained him a large number of friends who will long remember him "

Sir Henry married in 1906 Elizabeth Catherine, daughter of the late Sir William Ramsay, and she survives him with two sons and a daughter

CHARLES SINGER

M.A., D M., D Litt., Hon. D Sc Oxon., F R.C P

Dr Charles Singer, emeritus professor of the history of medicine in the University of London at University College, died on June 10 at his home in Cornwall

The son of the Rev Simeon Singer, a Hebrew scholar of distinction, he was born in London on Nov 2, 1876 He was educated at the City of London School and at University College, London In 1896 he became a scholar of Magdalen College, Oxford, of which he was afterwards an honorary fellow At Oxford he read zoology, but medicine was his aim, and he went on to St Mary's Hospital for his clinical training In 1903 he took the conjoint qualification, and straightway went, as medical officer, on an expedition under Sir John Harrington for the delimitation of the Abyssinian frontier with the Sudan On his return he held resident posts at St Mary's and other hospitals, and gained further experience in tropical diseases in a post in the Government General Hospital at Singapore In 1909 he began consulting practice and was appointed physician to the Dreadnought Hospital for Seamen He was also medical registrar to the Cancer Hospital, Brompton, and there made a study (with S B Schryver) of the chemical composition of the gastric juice in carcinoma and other diseases But he had already found time to write several papers on medical history and begin work *On the Development of the contagium vivum*, 1500–1750 In 1914 he gave up consulting medicine, and on Osler's invitation went to Oxford to start his life-work as a medical historian He and his wife, who shared his interests, set up a history of science room in the Radcliffe Camera

When the war came, Singer took a commission in the R.A.M.C He was first posted to Malta. While there he began some anthropological and archæological work with Sir Themistocles Zammit. In 1916 he was transferred to Salonika and pursued his studies in Byzantine and modern Greek. Such was his zeal and enthusiasm that Osler termed him "that Socratic gadfly" With his wife's help, through correspondence, Singer was able to publish the first volume of his studies in the *History and Methods of Science* After the war he returned to Oxford as lecturer in the history of the biological sciences In 1920 he was appointed lecturer in the history of medicine at University College, London, and in 1931 he was elected to the chair which he held till his retirement in 1942

Singer knew many languages He could read ancient and modern Greek, Latin, Arabic, Anglo-Saxon, French, German, Dutch, Italian, and Spanish This acquaintance with ancient and modern tongues was a great help in his work Among his chief works were *Greek Biology* and *Greek Medicine* (1922), *History of the Circulation of the Blood* (1922), *A Short History of Medicine* (1928), *Historical Relations of Religion and Science* (1928), *A Short History of Biology* (1931), and *A Short History of Science* (1941) He was one of the editors of the four volumes of the *History of Technology* (1954–58)

He was president of the third International Congress of the History of Medicine (1922) and of the second International Congress of the History of Science and Technology (1931) He gave the FitzPatrick lectures to the Royal College of Physicians on the evolution of anatomy in 1923–24 He was Noguchi lecturer at Johns Hopkins University and Mary Scott Newbold lecturer at Philadelphia in 1930 During 1931–32 he was visiting professor at the University of California He was elected F R C P in 1917 He was also Fellow of the Society of Antiquaries, an honorary fellow of the Royal Society of Medicine, and a fellow of University College, London He was a past president of the British Society for the History of Science, and the International Society for the History of Science He held the Oxford doctorates in the faculties of medicine, letters, and science, the D SC being an honorary degree The *Festschrift* presented to him in 1953 contained a detailed bibliography of his own writings, and 90 essays contributed by leading historians in Great Britain, the United States, and the Continent, which ranged from the twilight of history to the 19th century and after This work was later published as *Medicine, Science and History*

A MACN writes

"Charles Singer founded a school of historical research in medicine and science, illuminated it with scholarship, thought, and wisdom, and gave forth its lessons with eloquence and literary distinction He had a delightful personality He was kind and generous, scintillated with ideas for the improvement of mankind, and, as his work before and during the late war showed, was a friend to the oppressed. He helped to found the Society for the Protection of Science and Learning, and he and his wife rescued and succoured many victims of Nazi tyranny He was ever ready to pour out the stores of his knowledge to help the budding historian and others on the ladder of life His conversation was adorned with wit and humour, and he and Mrs Singer were delighted to entertain their friends—and of these there were many—at Kilmarth or in London The world is the poorer for Charles Singer's passing, but his works abide with us "

Professor Singer married in 1910 Dorothea Waley, daughter of Nathaniel L Cohen, who has won an international reputation as a medical historian in her own right

Prof ESTHER KILLICK

M F L K writes

"The untimely death of Esther Killick will be deeply felt, not only by members of the Royal Free Hospital School of Medicine and the University of London, but also in far wider spheres She was a woman of outstanding character and ability She had powers of leadership and analysis and also possessed great courage, calmness of judgment, and a precision of thought clear-cut as her admirable profile Endowed with these gifts she made a superb chairman or committee member, and as such she gave unstinting help to the Royal Free Hospital School of Medicine, the University of London, and many outside bodies Her habitual appearance was one of stillness and reserve which gave a false impression of aloofness, because those who really came in contact with her soon realised her friendliness, and those who sought her help and advice invariably found her a willing listener and a kindly mentor Moreover she and her husband, Prof St. John Huggett, and their children enjoyed an extremely serene and happy home life, which surely was the basis of her tranquillity "

Appointments

BAIN, A. D , M.D Edin. consultant pathologist, regional pædiatric pathology service, Royal Hospital for Sick Children, Edinburgh.
COOK, I A., M.D Aberd. consultant pathologist (hæmatologist) in charge, hæmatology department, and director of regional blood-transfusion service Royal Northern Infirmary, Inverness
JONES W W , M.B Belf., F.F.A. R.C.S., D.A. consultant anæsthetist, Glasgow Royal Infirmary
MCINTOSH, A. D , M.B. Edin., M.R.C.O G consultant gynæcologist and obstetrician, Lanarkshire maternity service
MOSS, B J L., M.B. Lond., D C.H., D.P H M.O.H., Leicester
RICHMOND, H. G , M.D Aberd consultant pathologist in charge, pathology department, Royal Northern Infirmary, Inverness
WILSON, P R., L.R.C.P.I. school M O , Cornwall.

The Hospital for Sick Children, Great Ormond Street, London

FORBES, C. E. M.D , B.SC. house-physician.
MCKAY, S R., M B. Melb , D T.M. & H. house-physician.
PARRY, G R., M.B. Lond., F.R.C.S. surgical outpatient assistant.
RENWICK, A. G C., M.B. Edin. registrar, department of chemical pathology

Notes and News

EMPHYSEMA AND BRONCHIOLITIS

SPEAKING to the Manchester Medical Society's section of pathology on May 25, Prof J Gough said that morbid-anatomical changes are much more clearly seen in lungs if these are fixed in expansion before they are cut This applies especially to certain forms of emphysema Centrilobular emphysema, for instance, is not always easy to identify at necropsy, but is clearly seen in the expanded lungs, especially if thin slices are examined The existence of this type of emphysema as a common finding has been confirmed in several places in Britain, and also in Australia and the United States It is due to bronchiolitis, but further studies are required to show whether this is always infective or may be caused by other agents from the atmosphere Thin sections of expanded lung show clearly the difference in the effects of spasmodic asthma and of chronic bronchiolitis In asthma the lungs are over-distended but usually there is no destructive emphysema, whereas with bronchiolitis the destructive centrilobular type is characteristic The airway obstruction of byssinosis is associated with changes indistinguishable from ordinary bronchitis, the accompanying emphysema being of destructive type

An observation of fundamental importance is that of Caplan who found distinctive radiological changes in the lungs of rheumatoid coal miners The pathological changes which underlie the radiological ones are also distinctive and show a combination of rheumatoid and pneumoconiotic lesions The interpretation of how certain dusts, especially coal dust, can render the lung vulnerable to the rheumatoid change seems a field for fruitful research

A condition which appears to be a new disease is Alveolar Proteinosis Among the 27 cases which comprised the first report in 1958 only one came from Britain, but since that time other cases have been identified in this country The condition is easily confused with pneumocystis carinii pneumonia, both in its radiology and its gross morbid anatomy The lesions, however, can usually be distinguished histologically without difficulty

OLD PEOPLE AN ESSAY IN COORDINATION

IT is almost a truism to say that the medical care of old people involves much beyond " medicines ", and that one of the greatest difficulties is in coordinating the many authorities and existing facilities At Sunderland General Hospital the department of medicine and geriatric medicine is to investigate the effect of combining some of these through a day hospital To this will be brought a random sample from five hundred former inpatients who are known to have been living alone after their discharge from hospital They are classified according to sex, and according to age (60–75, and over 75), and will be gathered from five districts—one for each day The effect of such a weekly visit to this special part of the department will be assessed by independent observers at intervals during the first eighteen months

The accommodation set aside has facilities for medical examination, ablution, chiropody, physiotherapy, occupational therapy, assistance from the almoner and from welfare officers, and meals during the day—for 1*s* 6*d* The local authority provides transport through the ambulance service, and the hospital provides medical, physiotherapeutic, and feeding services The hospital's league of friends helps with administration and with many of the extra services and comforts which will be needed All patients are seen in their homes by a health visitor and a doctor before the investigation and at three-monthly intervals

A grant from the scientific and research subcommittee of the Newcastle Regional Hospital Board covers the salary of a clerk, and contributes to preparation of the accommodation, but a great deal of the effort, and much economy in the cost, come from voluntary sources Apart from the undoubted benefit to these deserving patients, the investigation is an attempt to see whether the local health authority, the hospital service, the related branch of the Civil Service, and the voluntary organisations can be brought together to achieve a single purpose

COST OF BECOMING A DOCTOR

IN the United States, when the public complain (as they often do) about the high fees their doctors charge, the doctors point with some justification to the amount of cash (as well as hard study, responsibility, and so on) that their medical education has cost them, for, though the fees paid by students contribute only a minor fraction of the cost of running a medical school, those fees are much higher than the fees usual in Britain, moreover, they come after the similarly high fees paid for tuition at college, since two to four years' premedical college education is generally required

Some figures about this high cost of medical education, and its consequences, have been published by the Association of American Medical Colleges [1] The average cost of his four years' professional training to the 1959 graduate was $11,642 Many students obtain loans, and 81% hold outside jobs, often unconnected with their medical education; but financial help from families remains a big factor Only 16% of students had no such help, and over 80% of all the costs were defrayed by families This makes it inevitable that the medical schools have a high proportion of students from the wealthier families, thus the 11% of American families with an income of over $10,000 a year provided 43% of the medical students, and nearly half came from the median income-group with incomes of $5000–10,000

COLOUR TELEVISION DEMONSTRATION

A GROUP of lectures on Cell, Chromosome, and Virus Microscopy in Cancer Research, devised and coordinated by Prof A Haddow and Prof G J Cunningham, was presented at the Royal College of Surgeons of England by means of large-screen colour television on May 10

Dr E M F Roe, speaking from a distant studio, discussed photomicrographs of living cells taken with a normal microscope and phase-contrast, dark-ground, and fluorescence techniques Dr E J Ambrose showed normal and malignant kidney cells by interference microscopy and suggested that the apparent lack of adhesion between the cell membranes of the latter might be responsible for the spread of cancer Professor Cunningham demonstrated the technique for rapidly freezing cells to what he called the " nearly living " state Showing that there was an unusual deposition of fat in certain basal cells associated with abnormal tissues in normal bronchi, Professor Cunningham suggested that fat-soluble carcinogens might dissolve in this fat and initiate cancer

Dealing with the role of chromosomes, Prof P C Koller introduced a film which was projected in the lecture-hall He explained that the mitosis shown in the film could be arrested in the metaphase stage and the variations from the normal number of chromosomes associated with certain tumours could be analysed Dr S H Revell demonstrated the effect of radiation on chromosomes and showed how micronuclei were formed by the abnormal division of the chromosomes Finally, Dr R J C Harris discussed the role of the virus in cancer A virus grown on the embryo cells of a mouse can cause widespread cancer in hamsters and other animals

The excessive heat from the intense light caused considerable strain Is this wholly unavoidable? Why should a lecturer be separated from his audience by a couple of miles when it would be to their mutual advantage to be in the same hall? This is not to decry the usefulness of television the many demonstrations involving laboratory facilities and live animals to illustrate the lectures needed enlargement on the screen to be seen clearly by the huge audience But television, like the lantern-slide and film, is but a visual aid, and when the novelty is over, it will doubtless take its place with them

CONTRIBUTION OF SURGERY TO CLINICAL CARDIOLOGY

THE lecture that Mr T Holmes Sellors gave in Edinburgh last year is now obtainable from the publications department of the Royal College of Physicians, 9, Queen Street, Edinburgh 2 (4*s*, postage 6*d*) It was the George Alexander Gibson lecture of the college, and it concludes by saying that Dr Gibson, had he lived a few more years, "would have been able to see his observations and deductions proven at operation " One of the best contributions that surgery can offer the clinical cardiologist, Mr Sellors points out, "is the opportunity of seeing the pathological heart exactly as it is in the body"

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[1] *New York Times*, May 29

University of Oxford

On June 4 the following degrees were conferred

D.M —C J Dickinson, H C Nohl
B.M —Robert Cook

University of Cambridge

Dr L G Whitby has been appointed university biochemist to Addenbrooke's Hospital

University of London

Dr A J Buller, senior lecturer in physiology at St Thomas's Hospital Medical School, has been appointed to the readership in physiology at King's College, and Mr D F N Harrison, senior registrar to the ear, nose, and throat department at Guy's Hospital, to the readership in laryngology at the Institute of Laryngology

Royal College of Surgeons of England

At a meeting of the council on June 8, with Sir James Paterson Ross, the president, in the chair, Prof Carl Semb (Oslo) was admitted to the honorary fellowship Diplomas of fellowship were granted to the following

T E Jeffreys, R T B Jones, Delia M H Cothay, J L Somervell, J R F Ingall, J M Dolphin, J R Kirkup, *C G Keith, J H H Webster, P C Anderson, L J Lawson, D W Atkinson, Malcolm Swann, P R Hawley, M A Nelson H C Smith, Ratan Lal Agarwal, J W Eadie, D M Davies, D M Boyd, J N Cozens-Hardy, J D Sheils, Mohomed Nafick Burhan, *T D H Gray, †J A O'Reilly, Thethravusamy Joseph Aloysius, John Considine, F J Ensell, M R Mynhardt, Benarsi Lal Talwar, *Jagdish Sarup Gupta, K L Hayes, †K T Jones, A D Lyall, Rajendra Nath Mullick, C V Petersen, †Shrof Ramasetty Chandrasekha, I A Le G Ferguson, R L Garner, J N Gibson, M C T Morrison, Suniti Ratnakar Samsi, G A G Scarlett, Prakash Chandra Bansal, A P Blower, B W Broadhurst, D G Calvert, *J F Cullen, Amal Kanti Dharbhaumik, I S Lister, Pradip Mazumder, Mookkassanairveettil Pullare Achutha Menon, P J Molloy, Sein Myint, E P Simkin, Donald Solomons, G W Sprigge, R D Upton, *B J Bowden, E R Briant, G R Duncan, Muttukuttige Bernard Clement Perera Gunawardene, J E Handelsman, Labib Naiem Hasso, J D Iswariah, D R Kennedy, R J Kitchin, Jacob Thannikal Kuruvila, Michael Laurence, Sam Minocher Mahaluxmivala, Teja Singh Mangat, Ayub Khan Ommaya, R A Roxburgh, Chandramma Dayananda Sagar, Mohyie El-Din Sedky, H J K Vieyra, R C W Williams, Ruth Wynne-Davies, J G Allman, R C Bennett, D M Burgess, G V P Chamberlain, A C W M Da Roza, J R M Davidson, A C B Dean, Basil Gampel, A H Hackett, R M Hollings, †L K Jobbins, H R Johnson, D M King, †F W Kwock, J B Lynch, †R S McAlary, J B McFarland, Bharat Vrajlal Mehta, Vettivaloo Kandasamy Pillay, D J Reid, K F Ross, G B Smaill, Madho Prashad Vaidya, †I H Warner, M O Woo-Ming, Soorya Bahadur Basnyat, Suresh Vishvanath Bhave, Cheung-Ping Chan, G D Chisholm, Arvind Krishnalal Dangarwala, Arjun Dev, †W G Edwards, A J J Emmett, J I H Hadfield, I M Hamilton, Leo Lenaghan, F T McDermott, M H W Mullerworth, B F Reeves, J S Scougall, G A Syme, D F Weinman, Akinpelu Oludele Adesola, Manickavasagar Balasegaram, K A Butler, D M Essenhugh, H J H Fry, G R Gibson, Ann E Johnson, P W B Lane, †Wilfred Leach, J B Morris, E L Parry, P H Smith

*In ophthalmology †In otolaryngology

At a meeting on June 9, the Lady Cade medal was presented to Group-Captain R C Jackson, and the following were coopted to the council for the year 1960–61, representing various branches of practice

Mr T Keith Lyle, ophthalmology, Mr C Gill-Carey, otolaryngology, Mr H G E Arthure, gynæcology and obstetrics, Dr G S W Organe, anæsthetics, Prof M A Rushton, dental surgery, Dr John H Hunt, general practice, Prof D W Smithers, radiology

Dr Preston A Wade (New York) was appointed second Watson-Jones lecturer The Mitchiner medal for 1959 was awarded to Lieut-Col I A Walsh, and for 1960 to Major-General W D Hughes A diploma of fellowship was granted to C J Smallwood

Bequest to Birmingham University

The late Frank Barnes, F R C S, has left the residue of his £137,000 estate to the university "to be used exclusively for or towards the cost of the erection or upkeep or maintenance and improvement of the Medical School, including particularly the library and lecture room"

Royal Australasian College of Physicians

At a meeting of the general body of fellows of the college held in Melbourne on May 25, the following were elected and admitted to fellowship

Under article 44 F W A Clements, F C Courtice (New South Wales), D O Shiels (Victoria), Geoffrey Sydney Todd (England) *Under article 42* B A D Curtin, R I Eakin, E J Halliday, G L McDonald, J R Sands (New South Wales), A V Jackson, H I Jones, L Murphy, H P Taft, H E Williams, A Wynn (Victoria), R A Burston, J S Covernton, A K Grant, R Hecker, J M McPhie (South Australia), P L Dorney, F R T Stevens (Tasmania), G F Hall, W J Smith (New Zealand)

On May 23 the following were admitted to membership

O Appenzeller, A G G Bennett, L Brenner, D S Child, J M Duggan, N D Gallagher, B Haneman, A M Lloyd, M S Owen, B J Pascoe, R A Royle, J D Wingfield (New South Wales), H G Burger, K Catt, B S Faragher, J E Fitzgerald, J Hansky, A K Lethlean, I G Lyall, J F O Callaghan, S F Phillips, J G Sloman, R R W Townley (Victoria), J T Andrews, G T Ey, A J Watson (South Australia), K R Hayes, K P Kennedy (Queensland), B R Beveridge, B A Kakulas (Western Australia) *Under article 37* K F Anderson (South Australia), G M Watson (New South Wales), Saul Wiener (Victoria)

London Hospital Medical College

On Wednesday, July 13, at 5 15 P M, at the college hall, Ashfield Street, E 1, Sir Macfarlane Burnet will give the Schorstein lecture He will speak on the potentialities and limitations of tissue transplantations Tickets may be had from the secretary of the college, Turner Street, E 1

Lady Tata Memorial Trust

For research on leukæmia and allied diseases in the year beginning Oct 1, the trustees have made the following awards

Grants for research expenses —Dr B M Braganca (India), Dr J Pontén (Sweden), Dr M Simonsen (Denmark), Dr H J Woodliff (Great Britain)

Scholarships —Dr L Chieco-Bianchi (Italy), Dr J Hastrup (Denmark)

British Medical Association

Dain Fund —During 1959–60 there was again an increase in the number of applications A total of 46 cases were helped with grants amounting to £5238 Just under £5000 was received in donations, and the balance in hand at the end of the year was £446 Of the 15 new cases at least 10 are likely to need help for several years, and regular donations to the Fund are welcome

World Mental Health Year Conference

In connection with World Mental Health Year, a quadripartite conference on community mental health services is to be held on Oct 7 and 8 at the London School of Hygiene and Tropical Medicine, Keppel Street, W C 1, between the Central Council for Health Education, the College of General Practitioners, the Royal Medico-Psychological Association, and the Society of Medical Officers of Health Particulars may be had from the secretary of the society, Tavistock House South, W C 1

Hospital Service Plan

The unique circular building which houses the new head offices of the Hospital Service Plan was opened at 157, St John's Road, Tunbridge Wells, Kent, on May 31 by Sir John Charles, chief medical officer to the Ministry of Health, who commended the Plan as a "self help" organisation Sir Russell Brain, the chairman, said that the growth of the Plan had necessitated the move from London in search of larger premises

The Hospital Service Plan enables contributors to provide for private treatment in hospitals or nursing-homes, for specialists' fees, and for other expenses of illness It is organised by the London Association for Hospital Services and controlled by a council whose members are nominated by the British Medical Association, the three Royal Colleges in London, and King Edward's Hospital Fund for London (its original sponsors), who give their services without remuneration Commercial, industrial, and professional organisations have taken an increasing interest in it, and in the past five years the membership has more than doubled

London College of Osteopathy

The Leverhulme Trust Fund is providing scholarships to enable medically qualified men and women to study osteopathy at this college

These scholarships, valued at £625, will cover the cost of fees and maintenance during the four terms' full-time course which begins next October Particulars may be had from the secretary of the college, 24, Dorset Square, London, N W 1

Mental Health Services Investigation

P E P, the independent research organisation, has received a grant of £25,300 from the Nuffield Provincial Hospitals Trust for a study of the mental health services

The project, which will take three years, will inquire into the future content and pattern of services for the mentally handicapped, with special reference to the possibilities and difficulties of care outside the hospital and will include field studies in selected areas

Blood-transfusion in Europe

This year the Council of Europe is to use its coordinated medical fellowships for the study of the problems of blood-transfusion in Europe Three fellows will visit hospitals and blood-transfusion centres in different member countries of the Council and possibly in Switzerland The research will be carried out under the direction of Dr J Spaander, director-general of the Public Health Institute of Utrecht

Toxic Chemicals in Agriculture

Sir Charles Dodds has been appointed chairman of the Interdepartmental Advisory Committee on Poisonous Substances used in Agriculture and Food Storage, in succession to Sir Solly Zuckerman The committee was recently reconstituted and its members now include Prof J H Gaddum and Prof Andrew Wilson

A Regional Course in Psychotherapy

The North East Metropolitan Regional Hospital Board has approved a scheme for instruction in psychotherapy for doctors who are being trained in the region

Courses of twelve weekly seminars will be held at the Institute of Psychiatry, the Maudsley Hospital, by a senior staff member Each course will be limited to 8 doctors The board will reimburse the fees and travelling expenses to 8 selected candidates in the grades of registrar, senior registrar, and junior hospital medical officer Senior hospital medical officers and consultants will be expected to pay their own fees and expenses The first course began on May 4

Psychosomatic Medicine and Childbirth

An international congress on this subject will be held from Sept 12 to 15, 1961

It has not been finally decided where this meeting will take place, but the most likely places are Paris, Vienna, or Geneva The subjects chosen for discussion are psychological and sociological study of the woman in connection with her pregnancy, labour, and the puerperium, psychophysiology of the pain of labour, theory, practice, and results of combined psychological and physical preparation for labour, and the value and the limitations of the psychosomatic methods in obstetrics Those who wish to contribute are asked to get in touch with Prof Norman Morris, Charing Cross Hospital Medical School, London, W C 2

Teratology Society

For several years anatomists, biochemists, embryologists, geneticists, obstetricians, pathologists, pediatricians, plastic surgeons, and other scientists have held informal conferences on basic problems of congenital malformations, and after the fourth teratology conference, held at the Memorial Sloan-Kettering Cancer Center in New York City and attended by 76 scientists from Canada, England, France, Germany, and the United States, it was decided to form a society to hold regular meetings in which investigations into the ætiology and morphogenesis of congenital malformations could be presented and discussed Prof Josef Warkany was elected president and Dr Marjorie M Nelson secretary-treasurer Her address is department of anatomy, School of Medicine, University of California, San Francisco 22

Royal Institute of Public Health and Hygiene

Dr W A R Thomson will give the Bengué lecture on Wednesday, Oct 19, at 5 P M, at the institute, 28, Portland Place, London, W 1 His subject will be Doctors, Drugs, and Diseases

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On Friday, July 8, at 8 P M at the Midland Centre for Neurosurgery, Holly Lane, Smethwick, nr Birmingham, Dr A Huber of Zürich, will give a lecture on eye symptoms in brain tumours

On Tuesday, July 19, at 5 30 P M, at St Mary Abbots Hospital, Marloes Road, Kensington, W 8, Dr James Arnhoff, of the Mount Sinai Hospital, New York, will give a lecture on psychosomatic E N T problems

Under the chairmanship of Prof A V Neale, a joint committee of the Bristol division of the British Medical Association and the Bristol local medical committee have been studying " the prevention of break-up families " Copies of their report (5*s* 6*d*, post free) may be had from the local medical committee, 7, the Dell, Westbury-on-Trym, Bristol

Practical Dietetics—The series of articles which appeared under this title during 1959 in *The Practitioner* (5, Bentinck Street, London, W 1) have now been reprinted as a booklet (4*s* 6*d*) under the editorship of Dr W A R Thomson

The Cambridge Graduates' Medical Club will hold its annual general meeting and dinner at Pembroke College on Friday, July 1 Members who have not yet received notification, or other Cambridge men interested, should write immediately to H E Batten, F R C S, 67, Bridge Street, Cambridge

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Diary of the Week

JUNE 19 TO 25

Monday, 20th

University of London
5 P.M (University College Hospital Medical School, University Street, W C 1) Prof N C Louros (Athens) Reduction of Pain During Labour and Delivery
Postgraduate Medical School of London, Ducane Road, W.12
4 P M Dr Brian Ackner Anorexia Nervosa

Tuesday, 21st

Royal College of Physicians of London, Pall Mall East, S W 1
5 P M Dr J G Scadding Mycobacterium Tuberculosis in the Ætiology of Sarcoidosis (Mitchell lecture)
University of London
5 P M (London Hospital Medical College, Turner Street, E 1) Dr Austin T Moore (Columbia, South Carolina) Surgery of the Hip with Special Reference to Moore Arthroplasty

Wednesday, 22nd

Royal College of Surgeons of England, Lincoln's Inn Fields, W C.2
5 P.M Miss Jessie Dobson A Hitherto Undescribed Section of John Hunter's Museum (Arnott demonstration)
Postgraduate Medical School of London
2 P.M Prof S D Elek Cytomegalic Inclusion Body Disease
Institute of Dermatology, Lisle Street, W C 2
5 30 P M Dr R. W Riddell Infections Due to Yeasts
Institute of Diseases of the Chest, Brompton, S W 3
5 P.M Dr S W A Kuper B C G Vaccination and Leprosy
Royal College of Surgeons of Edinburgh, Edinburgh, 8
5 P M Prof Robert B Duthie (New York) Histochemistry of Bone Repair

Thursday, 23rd

Royal Society of Medicine, 1, Wimpole Street, W 1
2 30 P M *Urology* Mr W T Irvine, Mr J B Yule, Mr D G Arnott Absorption of Electrolytes Across a Colonic Mucosa Prof L N Pyrah Transplantation of the Ureters into an Isolated Rectum Sir Eric Riches Colo-cystoplasty Mr Richard Turner-Warwick Colonic Conduits
Postgraduate Medical School of London
4 P M Dr R. J G Sinclair The Marfan Syndrome
Institute of Child Health, The Hospital for Sick Children, Great Ormond Street, W C 1
5 P.M Dr Edith L Potter (Chicago) Perinatal Mortality Studies at the Chicago Lying-in Hospital
Institute of Dermatology
5 30 P M Dr Brian Russell Uncommon Skin Tumours, Clinical and Pathological
British Association of Urological Surgeons Home and Overseas
9 30 A.M (Royal College of Surgeons of England) Opening of two-day meeting

Friday, 24th

Royal Society of Medicine
8 15 P M *Obstetrics & Gynæcology* Professor Louros, Mr H P White, Dr D W Warrell, Mr C. A Simmons Urinary Incontinence in Women.
Postgraduate Medical School of London
10 A.M. Dr G W Taylor Primary Lymphœdema

The Lancet · Saturday 25 June 1960

MEDICINE IN ITS SETTING *

DOUGLAS HUBBLE
M.D Lond, F.R.C.P
PROFESSOR OF PÆDIATRICS AND CHILD HEALTH
IN THE UNIVERSITY OF BIRMINGHAM

Sir Leonard Parsons, first holder of the Birmingham chair of pædiatrics and child health, worked in a generation in which it first became apparent that the scientific method could be applied to the problems of disease in man But he understood that for doctors science was not enough —that man has a spirit which must be nourished and an environment which, by neglect or by ill-intention, had been allowed to become noxious both to man's body and to his mind He followed the way of scientific humanism, and this is a faith which inspires many of us in medicine and in science

Humanism was a stimulating philosophy in my youth its prophet was Lowes Dickinson and its poet Robert Bridges For later generations it has become a nearly discarded doctrine, since the direction of mankind has been diverted from the quest for virtue, beauty, and truth towards power, knowledge, and comfort It was suspect, too, as the rationalist's anthropomorphic substitute for religion, but it was in truth not exclusive of religion, but complementary to it Julian Huxley gave it a new appeal for scientists by preaching the doctrine of *scientific humanism* This did nothing to mitigate the dislike of the philosophers, the moralists, and the artists for this new wine in so ancient a bottle, for they had no confidence in the ability of science to construct a pattern for society Not without reason, they saw scientists as busily devising a great variety of destructive engines without concern for the consequences, and cheerfully sharing their secrets with children as immature as themselves

All the more need, I think, that those of us who practise medicine—even though we are derided as Victorian hangovers—should allow the principles of scientific humanism to determine our thought and conduct today We should pronounce a belief in the importance of the great human values and cherish the hope that science can help man to define and to achieve these objectives, both by controlling his environment and by increasing his knowledge of himself Events are moving swiftly, and if in our day there has seemed to be too much science and too little humanism, medicine and its associates are working—fallibly and falteringly—to prevent some of the foreseeable disasters for mankind

Medicine and Society

Medicine has a much clearer view of its responsibilities towards society than it had thirty years ago We have been compelled to move quickly, if not yet with as much foresight as the situation requires Even the physician in the fastness of his consulting-room has become aware of a change in his own reactions For example, the now accepted criticism that medicine should by this time have been able to prevent the common cold seemed to us a slightly derisory demand a generation ago René Dubos in his splendid book *The Mirage of Health* quotes the words of a physician that "it is part of the doctor's function to make it possible for his patients to go on doing the pleasant things that are bad for them—smoking too much, eating too much, drinking too much " Certainly, it was a surprise to us in consulting medicine to find that these behaviour disorders did not disappear by a five-guinea blast on our therapeutic trumpet And we began to observe that the correction of these bad habits was not easy for ourselves, unless our personalities had a touch of the masochist and the obsessional about them Later we became aware that diagnosis and prevention, at which we might make a shrewd guess in the individual, could only be determined for the community by population studies The departments of social medicine were ready to apply these techniques, and the Birmingham department has initiated many valuable inquiries, as have others in the school, notably J H Sheldon and Sir Arthur Thomson

Laboratory medicine and clinical science will undoubtedly identify the causes of the modern killers, but the therapeutic method to be employed must await our social diagnosis If we apply the principles of scientific humanism we shall find that our advice will be dictated by the need for the progressive amelioration of social conditions No-one would suggest that we should return to the insanitary conditions of the 18th century in order to prevent poliomyelitis, when we have an efficient vaccine Alternatively, no-one would wish, when science has identified the pathogen in our city smog, that we should be content to remove this substance from our smoking chimneys and immediately call off the campaign for cleaner air I cannot myself think that the precepts of scientific humanism allow us to sell contraceptive pills to the underfed millions when it should be possible to give everyone in the world 2000 calories a day (and maybe this ration allows optimal nutrition for the average adult) if we apply both our minds and our pockets to it Humanism, too, encourages us to accept mankind's little weaknesses (you recall the mild cynicism of the physician quoted by Dubos) and we shall, one of these days, remove the carcinogen from cigarettes in order that men and women may continue, unharmed, to make their contribution to aerial pollution We must be flexible then in our therapeutic approach to the ills of society

Much more foresight is demanded of us in detecting the undiscovered hazards for mankind They are multiplying rapidly and dangerously We may take some hope from the fact that the risks of irradiation have been so promptly and so thoroughly studied There are many problems that medicine has hardly stated, much less constructed a design for their investigation The advancing tide of mental disease finds us largely ignorant of its causes It is said that one in twelve of the population of the United States has had a schizophrenic episode (a statement that I find a little difficult to accept) and that by 1970 the incidence may be one in eight. Medical statesmanship will be required in the prevention of these community sicknesses Empirical action to persuade mankind to return to healthier ways of life may well be necessary before scientists have convinced themselves that the causes of such widespread diseases have been defined Rene Dubos makes this point well, and he instances the fact that improved sanitation was preventing infectious disease long before anything was known of bacteria A minor example of social action in advance of scientific proof was provided by the manufacturers of teething-powders who removed the mercury from their products before the scientists were convinced that the association of mercury with pink disease had been completely demonstrated—with the consequent disappearance of pink disease from the community

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* From an inaugural lecture delivered in the University of Birmingham on May 13, 1960

It may surprise my non-medical listeners to know that we are quite unaware of what constitutes optimal nutrition We are moving rapidly to maximal nutrition, so that we are growing taller and heavier in every decade, and puberty is being reached at still earlier ages Nobody has yet forecast how far this process will carry us, but already we can define the social difficulty which it creates, for sexual maturity has perforce to be matched to the educational and economic retardation imposed by our society These are psychological and social problems, but there may well be physical dangers involved in the maximal nutrition which we are on the way to attain

Medicine has had many an attack of conscience in recent years with the recognition that it has itself unwittingly created hazards for mankind We no longer take the Hippocratic Oath but its clauses have been built into our traditions

> "I will use treatment to help the sick according to my ability and judgment, but never with a view to injury and wrongdoing Neither will I administer a poison to anybody when asked to do so, nor will I suggest such a course"

We have erred in my own field of pædiatrics in which by the excessive administration of some drugs (e g , vitamins D and K) and by the unnecessary administration of others (e g , mercury) we have ourselves created disease when engaged in preventing it So severe has this lesson been that the Americans have given these doctor-engendered disorders a name—iatrogenic diseases (The Americans follow the Greeks in "having a word for it") These unhappy experiences should not encourage in us an excess of caution If a drug or an operation is likely to benefit our patients, then clearly the risks attendant on the treatment have to be assessed, acknowledged, and accepted All that our patients ask is that the treatment should be applied with all available skill, and with an awareness of its dangers

Society asks of medicine, then, more foresight in the appreciation of the hazards for mankind, and more humanism in the design of our therapeutic programmes, both for the individual and for the community

The Place of Medicine in the University

It is a truism, at least in medical circles, that medicine has a central position in a university, standing between the two cultures of art and science, having long established itself as a practical art, and being now in process of becoming an applied science

If medicine, however, wishes to make this claim, it is well for us to recognise the limiting factors in our position We should not wish to base this opinion on the fact that one encounters more doctors in the university staff club than members of any other faculty And it would obviously be excessive to regard ourselves as especially fitted to promote good relations in the university corpus Francis Bacon defined the Office of Medicine as "but to tune this curious Harp of man's body and to reduce it to Harmony" Medicine has no call to apply group psychotherapy to the "curious harp" of university life in order to reduce it to a discreet harmony

If indeed the position of medicine is central, then pure science is far out on the left wing and the fine arts away on the right wing (no political connotations are intended by these fanciful descriptions) The number of departments with which medicine collaborates is steadily increasing This is not only due to the extension of our own applied science towards physics, chemistry, genetics, microbiology, and zoology, but sometimes, as in the organ analysis of the chemists, because the scientists are taking an increasing interest in us

But this great bulge of medicine is increasingly towards the left, and our contacts with our friends in the arts are disappointingly meagre Social studies, education, and physical education—the list is a short one, and these are subjects, like our own, in which method is being applied to the study of man in his environment

The need for a bridge between the Two Cultures—as C P Snow dubbed them in the Rede lecture of 1959—cannot be denied, and yet I have found plenty of evidence in Birmingham, and I do not doubt that it could be found also in Cambridge, that the position is not quite so desperate as Sir Charles Snow pictured it The scientists use their books as tools, it is true, but they read also to "enter another world than theirs", and you will readily appreciate that the wheel has come full circle now that scientists are devising jokes about their own illiteracy, just as the Aberdonians, most generous of Scotsmen, delight to tell stories of their meanness You will recall the anecdote of the scientific visitor at Harwell who, when asked to sign his name, put two crosses in the book "Why the second cross?" asked the receptionist "That's my PH D ," proudly replied the scientist

Nor should we underestimate the capacity of the artists —historians, painters, musicians, theologians, English scholars—to understand what the scientist is talking about Arnold Bennett read *Nature* every week and claimed that he understood enough to make it worth his while to do so My friend and colleague, T J B Spencer, in his brilliant inaugural lecture, dealt with *The Origin of Species*, *The Descent of Man*, and *The Decline and Fall of the Roman Empire*, and proved that a professor of English may understand the significance of historical and scientific works as well as, or better than, do the historians and scientists themselves

In Snow's analysis of the gap between the Two Cultures there seems to be some confusion between the understanding of the scientific steps which are required to arrive at a conclusion, and a comprehension of the significance of the conclusion itself, it is not necessary to understand the former before one can comprehend the latter Proponents of the Two Culture theory omit a further consideration When a major and radical scientific hypothesis is first propounded—such as Einstein's relativity, or Yang and Lee's contradiction of parity (used by Snow as an index of the failure of communication between Science and the Arts)—only a few men in the whole world understand it, but in ten years it becomes part of the honours course curriculum, and by this time its importance in the scheme of things can surely be communicated to theologians, to musicians, and to doctors What was a pioneer climb for the skilled mountaineer becomes, in C E Montague's phrase, "an easy day for a lady" Fortunately our scientists have not disdained the practice of communication. Eddington, Jeans, Julian Huxley, Hoyle, and Medawar have all been ready to explain to the artist and the common man "the way of a serpent on a stone, the way of a ship on the sea, and the way of the stars in the heavens."

Nevertheless there is a need for improved communications within the university and this is recognised in Birmingham. It is hoped, for example, that the newly established second chair of theology will be taken by a professor who is cognisant of the major conclusions of science. There is now in the university a Broader Education Course for all undergraduates at the conclusion of their summer examinations. Such a scheme is indeed no more than a laudable therapeutic attempt to correct the educational atrophy which has developed in the schools as a consequence of the unnatural hypertrophy which was itself induced by university requirements. I am sure that the Crowther report *15 to 18* and the Gulbenkian report by A. D. C. Peterson of the Oxford University Education Department have been well studied in the faculties of the university. Both reports plan the reform of the 6th forms, one of their objects being to give us a student with a better general education. In medicine, we should be delighted if our students could have reached advanced levels in English, in mathematics, in one language, and in one scientific subject (physics or chemistry) before they undertook their work for the 1st M.B. I cannot see how this can be achieved unless our students come to their medical studies one year older than they do today, and for my part I think this must be accepted. If the money is there, and if the teachers, the classrooms, and the laboratories are there, the practice of medicine in this country would be greatly improved by the wider and deeper education of our students before they reach us. We are by no means alone among university departments in complaining that our students are inadequately educated. Such a reform of 6th-form education should do something to diminish the dangers of the "cultural divide" of which C. P. Snow has written, for this cultural division begins in the higher forms in our schools.

It is vain to hope that there will ever be a completely interchangeable language even among scientists themselves. For example, I am told that the physicists do not comprehend fully what the mathematical physicists are saying. The day of the universal scientist is over. The field is both too vast and too detailed and time is denied us. I have just been reading a book, *Significant Trends in Medical Research*, which describes an experiment in communication between medical scientists. Ciba House, to celebrate its tenth birthday, invited 30 distinguished medical scientists, among them 7 recipients of Nobel prizes, to listen to twelve papers describing advances in medical science. Although the experiment was a success, an analysis of the discussions shows that universal comprehension was not achieved. It could not have been expected, for example, that the physicians present would enter freely into a debate on molecular structure or on the chemical basis of virus multiplication. And yet there were many indications that, if the practice of communication is conscientiously pursued, improved understanding will come. Sir Harold Himsworth suggested at the symposium that medicine and its neighbouring sciences are rapidly becoming one "intellectual continuum." Here a common language is becoming a professional necessity.

Medicine, I conclude, has moved to the left, in this generation, away from the arts. If it seeks to regain its central position in the university it will have to work its passage to the right. A better general education for our medical students would help. A conscientious practice of communication and, even more important, a willingness to listen to voices other than our own are required. In the expansion of the university, medicine should stimulate the Enlightenment † to call in the Old World of the arts to redress the balance of the New World of science. I hear exciting talk of a new chair of architecture, a department of drama, and the building of a theatre. Those who view these developments with tepid appraisal may listen to the Sage of Edgbaston speaking a hundred years ago. The practical end of a university course, he wrote,

> "is that of training good members of society. Its art is the art of social life, and its end is fitness for the world. . . . It does not promise a generation of Aristotles or Newtons, of Napoleons or Washingtons, of Raphaels or Shakespeares, though such miracles of nature it has before now contained within its precincts. Nor is it content on the other hand with forming the critic or the experimentalist, the economist or the engineer, though such too it includes within its scope. But a University training is the great ordinary means to a great but ordinary end; it aims at raising the intellectual tone of society; at cultivating the public mind, at purifying the natural taste, at supplying true principles to popular enthusiasm and fixed aims to popular aspiration, at giving enlargement and sobriety to the ideas of the age, at facilitating the exercise of political power, and refining the intercourse of private life."

Although I think John Henry Newman might well have been surprised by the "fitness for the world" displayed by our science graduates, yet we cannot hope that our modern universities will produce the cultivated man of Newman's dream unless they given an enhanced importance to the faculties of the arts. Medicine, perhaps more than any other profession, has need of the cultivated man and the good citizen. Here its position in the university, if not central, is at least focal.

The Internal State of Medicine

May I add a few final words about the internal state of medicine? If you have agreed that the end of university education is to produce a good member of society, I hope you may agree too that the object of the medical course is to make a good doctor. This will appear to many of you to be so obvious an ideal as to be unworthy of emphasis. But it carries with it some important conclusions. It implies that, whether a medical student later becomes a general practitioner, a medical scientist, a surgeon, or a statistician, he is first trained to be a good doctor, that he learns both the method of science and the way of humanism, that he is taught how to handle the bodies and minds of sick people, whether he is to earn his living in a laboratory, in an insurance office, or in the homes of his patients, that we do not require two or three different sorts of medical education, and that there are no grades in the medical hierarchy. The fact that only 30% of our students become general practitioners is therefore not a matter for congratulation (moreover the country requires many more of them for a better family-doctor service), nor should it have any effect on our plans for the medical curriculum (despite the recommendation of the Goodenough Committee in 1943). When we discuss the medical curriculum, it is important to know what sort of a doctor we are setting out to make. The splendid report of the Medical School Planning Committee for

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† I use Enlightenment, rather than the Establishment, to describe our University rulers—a name that should encourage both the governors and the governed.

Rhodesia and Nyasaland ‡ owed some of its success to the fact that the committee had a clear notion of the kind of doctor the Federation required

When I assert that the purpose of medical education is to produce a good doctor, I mean by a good doctor a man or woman who is well aware of diagnostic possibilities, who knows what treatment should be given and who should provide it (whether he or another), who is quick to understand our changing human situation—one who carries charity in his heart and who is not repelled by the quirks, the follies, and the vices of mankind I take it that this good doctor is well fitted to be the "personal doctor" of whom Dr Fox was writing in *The Lancet* a few weeks ago I meet him, as I hope you do, when I consult my family doctor, when I am carried into the operating-theatre, and when I discuss a patient's problem in the department of experimental pathology It would be a bad day for medicine and mankind if we conducted our medical training with any other objective than this There is much talk of the dangers of increasing specialism and of our failure to regard the whole man, but these admitted hazards will be largely reduced so long as all these specialists begin their professional life as good doctors, men nicely compounded of science and humanism

I have no intention of discussing medical education in detail but I have three comments to make

The first is that we need not change our system because the General Medical Council has given us permission to do as we please At breakfast the other day I sat next to a professor of physiology from South Africa, and he astounded me by the information that their students were now to have an additional year's instruction in anatomy and that he approved the change Like all physicians and general practitioners, and many surgeons, I believe that in some medical schools too much time is already given to anatomy in undergraduate education The South Africa intention compels the conclusion that too often we discuss medical education in subjective, unscientific terms, sometimes dominated by the powerful expression of vested interests

This leads to the second comment, that we require more controlled experiments as to the results of our present educational methods, and a comparison of the results of different methods already in being, to decide the question, for example, of whether or not it is valuable to give our students some basic pathology before putting them to their clinical studies

The third is that we should get ourselves taught to teach We have university departments of education and we might ask them to give us some instruction in practical pedagogy I suspect that this has not been done before because we are nervous lest we should be concussed by discussions of learning theory

The question of specialism is engaging the attention of those of us who practise pædiatrics I have no doubt in my mind what is the pattern of the future The pædiatrician in a small centre is a general physician applying himself to an age-group whose problems are different from those of the adult He must maintain the closest contacts with general medicine With the better education of the medical student in pædiatrics he will increasingly find himself surrounded by family doctors who are well equipped to handle the common disorders of children—medical, psychological, and environmental He should see that these family doctors maintain their competence in pædiatrics, and he should encourage them to do the work which he, alone maybe in his area, was fitted to do ten and twenty years ago

The teaching-hospital pædiatrician should have quite a different orientation He must maintain his interest in general pædiatrics because he has the job of teaching medical students, but he should at the same time become expert in a special branch of medicine—metabolism, genetics, cardiology, neurology, hæmatology, endocrinology, or psychiatry He must be recognised as a specialist in his field, not only by his colleagues inside the hospital, but also by kindred specialists in adult medicine We know that children in the first year of life are better cared for in our hospital than anywhere else, but this will not be a sufficient justification in the next generation for the maintenance of a large general hospital for children When I left adult medicine to become a pædiatrician, some of my physician friends told me smilingly that pædiatrics was a dying branch of medicine This could only be true if the pædiatricians themselves fail to appreciate their opportunities I need not remind you of the increasing recognition that many adult disorders strike their roots in childhood If we fail to explore this unmapped territory ourselves many specialists in other disciplines will be eager to do so

Pædiatrics is but a domestic affair, by comparison with some of the large issues which I have been discussing Yet its problems illustrate well enough the progressive adaptations which are required of medicine We have not been endowed with the gift of prophecy, and yet we must contrive to forecast the future We must extrapolate our course with as much accuracy as we can command We must use every device, too, to reduce the rigidity of the framework in which medicine finds itself today Thus something to mitigate the appearance of inflexibility of the National Health Service was done when one man was whistled out of the tram in which he was happily riding "in predestined grooves" and was put in charge of a small bus in this great university

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‡ Published in full as a supplement to *Central African Journal of Medicine*, June, 1958, summarised in *The Lancet*, 1958, i, 270, 1958, ii, 218

FURTHER REMARKS ON THE FUNCTIONS OF THE BASAL GANGLIA*

J Purdon Martin
M A, M D Belf, F R C P
CONSULTING PHYSICIAN
TO THE NATIONAL HOSPITAL, QUEEN SQUARE, LONDON, W C 1

On a previous occasion I discussed two individual symptoms—hemiballismus and muscular rigidity—which, judged by their anatomical associations, were evidently disorders of function of the basal ganglia, and I made some deductions about the organisation and physiology of the basal ganglia (Martin 1959) Now I wish to discuss another symptom—intention tremor This may or may not be a disorder of the basal ganglia, but in any case it throws a light on the other symptoms, and so, indirectly, has implications regarding basal gangliar function

Postural Fixation

I shall have to refer more than once to the function of postural fixation

If I hold my arm horizontally in front of me, it has to be fixed in that position by the action of muscles around the shoulder, and it has to be held extended by muscles in the arm itself The muscles of the back and of the neck help to maintain the posture, and in fact all the muscles of the trunk and legs share in the activity The centre of gravity of the trunk moves backwards to compensate for the weight of the arm in front, and the muscles of the other arm may also make compensatory adjustments Though I use the words "fix" and "fixation" I do not mean to limit their application to conditions of immobility When the hand is moved about, the arm is still sustained at the shoulder and other joints, the supporting muscles at the shoulder and in the arm adapt themselves to the movement, and muscles all over the body make appropriate modifications of their postural activity In the process the centre of gravity is continuously adjusted All this is done unconsciously, and apparently by mechanical processes

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* Part of a lecture with films given at the National Hospital, Queen Square, during the centenary celebrations (June, 1960)

If a patient has a lesion of one cerebellar hemisphere the muscles in the same half of his body become hypotonic, and he then fails to fix his outstretched arm firmly It can too easily be displaced from the maintained position, and it rebounds unduly when displaced. But, what is more important, it is imperfectly supported for movement—with the result that the hand sways in the course of the movement, and at the end of a movement the exactness of its control is lost. The adjustments of the musculature of the trunk and of the legs are similarly disordered. This hypotonia and ataxia constitute a negative, or defect, symptom—a disorder due to something lacking in the movement. One mechanism of postural fixation depends, then, on the cerebellum

Of more fundamental importance is the mechanism which supports our bodies against the action of gravity The principal nuclei of this system are in the brain-stem (see summary in Magoun 1958), and they are associated with complex apparatus in the spinal cord and muscles The postural reflexes also, in wide variety, bring about automatic adjustments of these mechanisms

Recently I have had reason to believe that there is another mechanism of postural function, and I wish to consider in this connection intention tremor, hemiballismus, and muscular rigidity and the effects on them of stereotaxic operations

Intention Tremor

Under this heading I do not include all tremors that happen during movement, but only the characteristic intention tremor, seen in disseminated sclerosis and in few other conditions

This tremor is a side-to-side movement which appears when the patient begins to make a "directed" movement. He fails to fix his limb normally at the proximal joints, and the more he tries the worse the shaking becomes It increases in amplitude as the movement nears its object, and the more precise the intended movement the worse the tremor, it increases if the patient tries to touch a target. Nevertheless, the patient may make an aimless movement without tremor, or if he allows his relaxed limb to be moved passively no tremor occurs

In man intention tremor ordinarily arises in cases with multiple lesions, and so the lesion responsible cannot be identified In the monkey intention tremor—called by Carpenter "ataxic tremor"—is particularly associated with experimental lesions of the dentate nucleus (Carpenter 1958), and it is accompanied, especially in the early postoperative stages, by ataxia and simple tremor

It has now been shown that intention tremor, like hemiballismus and muscular rigidity, can be abolished by a surgical lesion in the ventrolateral nucleus of the thalamus (Irving Cooper 1960, Dimsdale and Bennett 1960, McCaul and Martin 1960) As far as I know no surgeon has attempted to abolish it by a pallidal lesion, and so it is not known whether such an operation would be effective

In the monkey, Carpenter has shown that lesions destroying the dorsal division of the ansa lenticularis (i e, fasciculus lenticularis) abolish both simple and ataxic tremors contralaterally Lesions of the globus pallidus reduce both ataxic and simple tremors "they seem to be more effective in ameliorating ataxic tremor than simple tremor, while ataxia and synergic disturbances are not greatly modified" (Carpenter 1958) Thus it seems probable that the thalamic operation abolishes intention tremor by producing a pallidofugal block, although *clinical* evidence of direct association with the pallidum is still lacking

As with hemiballismus and rigidity, when intention tremor is abolished by operation, voluntary movement in the previously affected limb seems normal (in the absence of other causes of disability) There is, therefore, no disorganisation of voluntary movement while intention tremor is present, but the tremor is superimposed on voluntary movement In these features intention tremor closely resembles hemiballismus (Martin 1959) Further, when intention tremor, which is a disorder of fixation of a limb for movement, is abolished by operation, a normal or at least adequate power of fixation remains There were, therefore, at least two fixation mechanisms—a disordered one which has been put out of action by the operation, and one or more normal ones which remain and provide fixation which is adequate for all ordinary purposes

Again, because the disordered mechanism is characterised by intention tremor, we can before operation see when it is in action. The tremor appears as soon as a directed voluntary movement is initiated, and the more precise the movement the greater the tremor—indicating that the disordered mechanism is more active This would be expected of any adjustable fixation mechanism since the more precise the movement intended, the firmer and more exact is the fixation required, and therefore the greater the activity of the fixing mechanism. I will not carry the argument further with regard to intention tremor Suffice it to say that the disordered mechanism comes into action with a directed voluntary movement, and especially for its most precise part.

Hemiballismus

If we now consider hemiballismus in the same way, it becomes clear that it too is a disorder of fixation It is a "positive" or release phenomenon, in which the muscular mechanism responsible for fixation of the limbs and trunk is acting wildly † Its relation to fixation is perhaps more easily seen when it is reduced by sedation to a state in which it is abolished while the patient is at rest but appears again as soon as the patient begins to make a voluntary movement, it is then apparent that the limb, far from being supported normally at the proximal joint for the movement, is moved about involuntarily at its base.

The anatomical associations of hemiballismus are more clearly defined than those of intention tremor We know the site of a lesion that will bring it on and we know the site of a lesion that will abolish it—both in the basal ganglia Judged by its anatomical associations, hemiballismus is a disorder of function of the basal ganglia, regarded clinically it is a disorder of fixation. Hence the basal ganglia must be concerned with postural fixation

Further, a lesion in the pallidum or the operation of pallidofugal block abolishes the involuntary movements, and the patient can then move the previously affected limbs normally As before, there must have been at least two fixation mechanisms, one of which was disordered, and in this case the disordered mechanism may be interrupted by an operation on the globus pallidus There is therefore a fixation mechanism which is dependent on the globus pallidus This is the same conclusion as before, but in its converse form Moreover, the patient is left with adequate power of fixation in the previously affected limbs there is no sign that the operation has interfered with the cerebellar or anti-gravity mechanisms Thus the fixation mechanism dependent on the basal ganglia appears to be distinct from the cerebellar and anti-gravity mechanisms

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† I have always accepted that hemichorea or hemiballismus was a release phenomenon, but I have never until now been able to discover what function or what mechanism was released The fact that it is due to release of a fixation mechanism explains why hemiballismus, regarded as a chorea, has its peculiar incidence on the proximal muscles

Muscular Rigidity

Not much imagination is needed to see that muscular rigidity, too, is a disorder of fixation The patient is suffering from too much fixation—overaction of the fixation mechanism—with consequent widespread tonic overactivity of his muscles, and, often, disturbance of the control of his centre of gravity

I have argued previously (Martin 1959) that hemiballismus and muscular rigidity are different disorders of the same (basal gangliar) mechanism—the one depending on discontinuous innervation of the musculature and the other on a uniform continuous innervation In hemiballismus the corpus Luysii is damaged, in muscular rigidity it is intact In both the muscular overactivity may be abolished or reduced by pallidal lesions or by pallidofugal block

A surgical lesion in the globus pallidus relieves muscular rigidity but does not produce hypotonia, and it leaves normal or at least adequate power of fixation Hence it evidently interferes with a mechanism that is responsible for the excess tone—an additional tone-producing or fixation mechanism (Martin 1959)

Once we accept that muscular rigidity is a disorder of postural fixation, all the previous arguments apply On the one hand it is a disorder of function of the basal ganglia, and on the other it is a disorder of fixation, hence the basal ganglia are concerned with fixation Conversely, a mechanism of fixation and tone is interrupted by a pallidal lesion, hence such a mechanism is dependent on the globus pallidus But in this case we must say "dependent on the basal ganglia", because the corpus Luysii must be relatively intact as well

Negative Symptoms

These various disorders that I have considered are "positive symptoms"—i e, they consist of something added to the normal—and, of course, nearly all the symptoms that we associate with disease of the basal ganglia are of this character The study of these positive symptoms leads us to believe that the basal ganglia are concerned with postural fixation, and that they provide one of the fixation or supporting mechanisms of the body

But negative effects also are known, both experimental and clinical, although I have no personal observations of this kind to offer As far as I know they all depend on bilateral destructive lesions of the globus pallidus

Carpenter et al (1950) did not observe any defect of function in animals resulting from unilateral pallidal lesions (apart from an inconstant "feeding preference" for the unaffected hand), but very severe symptoms appeared when the second side was operated on, the animals being unable to stand In later experiments Mettler (1957) observed that the animals retained any posture that was imposed upon them Denny-Brown (1960) has described very similar effects, some of his animals eventually learned to stand when placed on their feet but their heads would gradually sink and at times would rest on the floor Denny-Brown has also described extreme postural disturbances—astasia-abasia and immobility—in man, associated with severe bilateral pallidal lesions following coal-gas poisoning, a condition which has a selective (though not exclusive) incidence on the globus pallidus

The effects of unilateral operations might lead us to regard the mechanism that has been interrupted as merely a supplementary one But these reported effects of bilateral destruction of the globus pallidus show that the postural mechanism contained in the basal ganglia as a whole is of fundamental importance

Some degree of bilateral damage, however, may be tolerated, and perhaps better by man than by the monkey

Yakovlev's (1944) patient, who had large bilateral pallidal lesions following coal-gas poisoning, seems to have gone for many years without any very disabling postural or motor disturbances, other than some disorder of gait, and recently a number of patients have had bilateral operations—either pallidectomy or pallidofugal block—without lasting disability Thus the approximate amount of globus pallidus which must be intact and functioning to preserve anything like normal postural activity, and the extent to which other fixation mechanisms may compensate for deficiency of function of the basal ganglia, are still undetermined

Bilateral Action of the Globus Pallidus

I have more than once mentioned that after a unilateral operation for intention tremor, hemiballismus, or muscular rigidity, voluntary movement in the previously affected limbs seemed normal, and this accords with experimental observations Since the effects of severe bilateral pallidal lesions in the monkey are out of all proportion to those of unilateral lesions, it is evident that after the unilateral operation the animal depends largely on the remaining (intact) globus pallidus, and so the action of that (and therefore of each) pallidum must be, to a significant degree, bilateral

In so far as the action of the globus pallidus (and therefore of the basal gangliar mechanism) is abrogated by operation, it can evidently be done without on one side The patient then has at his disposal for support of the previously affected limbs—first, any residual activity of the pallidum of the operated side, second, the ipsilateral action of the non-operated globus pallidus, and, third, the other fixation mechanisms and experience shows that these provide fixation that is adequate for all ordinary purposes

Conclusions

Intention tremor, hemiballismus, and muscular rigidity are disorders of postural fixation

Hemiballismus and muscular rigidity, judged by their anatomical associations, are disorders of function of the basal ganglia, and so the basal ganglia are concerned with postural activity

While these and other disorders of basal gangliar function commonly met in clinical neurology are "positive" symptoms (i e, due to excess activity), negative effects also are known, both in experimental work and clinically, and these severely impair postural functions

The evidence from both positive and negative disorders, therefore, indicates that the basal ganglia provide one of the postural supporting or fixation mechanisms of the body

The action of each globus pallidus is, to a significant degree, bilateral

The interactions of the basal gangliar mechanism with other postural mechanisms, and subjects such as the possible diversity of its relation to voluntary movement, and its relations to emotion and emotional movement provide obvious material for further study

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SUBDURAL HÆMATOMA

A REVIEW OF 389 CASES

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THE general rise in the age of the population and the steady increase in all varieties of trauma, make the problems of subdural hæmatomas progressively more important Hence it seemed valuable to review the clinical presentation, the surgical management, and in particular the prognostic features, of these lesions Accordingly we have reviewed 389 cases of proven subdural hæmatoma admitted under the care of one of us (W McK) to Leavesden Emergency Hospital, Atkinson Morley's Hospital, or the National Hospital, Queen Square, between 1940 and 1958 Cases in which the subdural lesion was insignificant or had resulted from rupture of a vascular anomaly were excluded

Classification of subdural hæmatomas into acute and chronic groups is time-honoured, but the definitions vary considerably Munro (1942) uses the term acute in cases with "evidence of fresh or unhealed brain injury", whereas Logue (1951), Dressler and Albrecht (1957), and others classify them on a purely temporal basis All systems of classification are imperfect, but we found that the rate of evolution of symptoms most accurately reflected prognosis We therefore decided to term "acute" those cases presenting urgent symptoms within three days of trauma, "subacute" those presenting within four to twenty days, and chronic those presenting after twenty days Cases with no history of trauma were classified according to total duration of symptoms

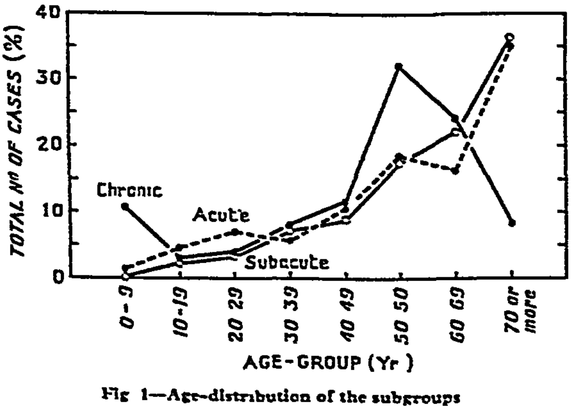

Fig 1—Age-distribution of the subgroups

Clinical Features

Age-incidence and Mortality

Because the numbers of the three types of hæmatoma were different, the figure for each ten-year period represents the percentage incidence of the total for the particular type of lesion thus the figure 30 for chronic subdural hæmatoma in the sixth decade represents 30% of all the chronic cases in the series (70 of 213 cases)

Fig 1 shows that the age-incidence in the acute and subacute lesions increases steadily, becoming maximal at and after seventy years In the chronic hæmatomas apart from those in infants, the incidence reaches an earlier peak. But the subsequent decline might be partly due to failure to diagnose the lesion, particularly in cases without a history of trauma in whom the alternative diagnosis of cerebrovascular disease may have seemed an adequate explanation for the symptoms

The relation of mortality to age in each subgroup is shown in table I

TABLE I—AGE-INCIDENCE AND MORTALITY IN 389 CASES OF SUBDURAL HÆMATOMA

Age-group	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70 –	Totals
Acute	1 *(0)*	4 *(0)*	6 *(2)*	5 *(1)*	9 *(5)*	15 *(10)*	13 *(5)*	29 *(21)*	82 *(44)*
Subacute	0 *(0)*	3 *(1)*	4 *(0)*	7 *(0)*	8 *(0)*	16 *(4)*	20 *(4)*	33 *(9)*	91 *(18)*
Chronic	22 *(2)*	6 *(0)*	9 *(0)*	17 *(0)*	25 *(0)*	69 *(3)*	51 *(5)*	17 *(3)*	216 *(13)*
Totals	23 *(2)*	13 *(1)*	19 *(2)*	29 *(1)*	42 *(5)*	100 *(17)*	84 *(14)*	79 *(33)*	389 *(75)*

(Deaths indicated in parentheses)

Clearly advancing age is associated with an increasing mortality-rate in all groups, and is therefore a very important prognostic factor The striking advantage of youth is shown by the mortality-rate of 8% among the 84 patients under forty, whereas it was 23% in the 305 patients over forty.

Subdural hæmatomas were frequent among older patients The incidence of hypertension is of interest because these patients are prone to injury It might also have prognostic significance. The findings were

	Hypertensive	*Normotensive*	*Unknown*
Acute	24 *(13)*	50 *(25)*	8 *(5)*
Subacute	30 *(5)*	58 *(12)*	3 *(1)*
Chronic	45 *(5)*	156 *(6)*	10 *(2)*

(Deaths in parentheses)

Thus the number of patients with hypertension was not unduly high A raised blood-pressure seemed to have an adverse effect only in the chronic group, and it did not alter the outcome in the others

Sex-incidence

The sex-distribution was

	Male	*Female*
Acute	54	32
Subacute	49	42
Chronic	162	54

The proportion of males was much greater in the chronic group, suggesting that additional factors operate in the production of chronic lesions as opposed to the more acute ones

Ætiology

"Major trauma" indicates an injury of sufficient severity to cause loss of consciousness, whilst "minor trauma" includes all lesser degrees of injury

	Major trauma	*Minor trauma*	*Cough*	*None*
Acute	52 *(32)*	30 *(12)*	0	0
Subacute	42 *(7)*	40 *(8)*	0	9 *(3)*
Chronic	51 *(1)*	73 *(8)*	4 *(0)*	86 *(4)*
Total	145 *(40)*	143 *(28)*	4 *(0)*	95 *(7)*

(Deaths in parentheses)

In the 4 patients in whom "cough" was regarded as a causal factor the symptoms started during a paroxysm of coughing The possibility naturally arises that some cases

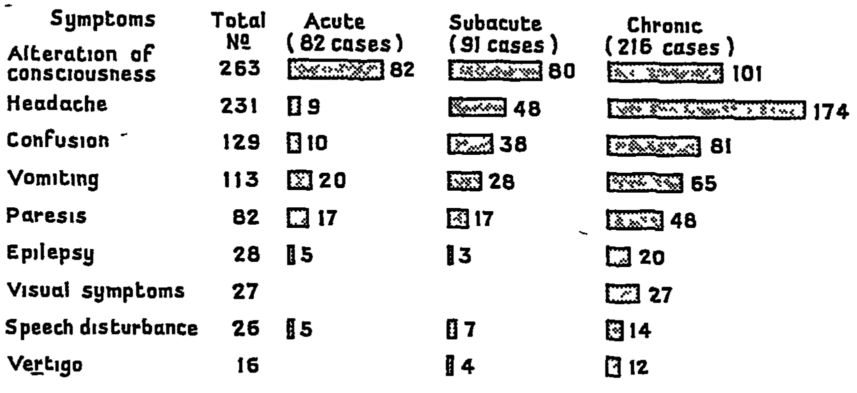

Fig 2—Frequency of symptoms in the subgroups

of "cough headache" may be due to subdural hæmatomas The table shows that the mortality associated with major trauma is higher in acute cases than in subacute or chronic ones The patients with minor trauma show clearly that the rate of evolution of the neurological picture is of more constant prognostic significance

Symptoms and Signs

The symptomatology shows certain natural trends (fig 2) The striking feature is the non-specific nature of the symptoms Alteration in the level of consciousness was prominent in the first two groups and headache was frequent in the chronic group, though of course changes in consciousness may preclude a history of headache 19 patients gave a clear history of unilateral headache, and in all of them the lesion was on the same side as the pain Epilepsy had pre-existed in 14 cases, and in the other 14 it was attributable to the subdural lesion Symptomatic epilepsy was therefore uncommon

Similarly the neurological signs on admission were of limited value in diagnosis (fig 3)

When the clinical state at the time of admission to the neurosurgical department is compared with that causing admission to the referring hospital, it is evident that alteration in the level of consciousness was the commonest cause for transferring the patient In a significant number of chronic cases the level of consciousness deteriorated between the times of admission and transfer to a neurosurgical bed A similar comparison shows an increase in paresis in all groups In the acute cases this is perhaps inevitable, but in the subacute and chronic groups it suggests unnecessary delay

In cases with pupillary inequality the dilated pupil was on the side of the lesion in 79% and contralateral in 8% In 13% the lesions were bilateral, and the larger pupil was usually on the same side as the larger hæmatoma

Paresis was an even less reliable sign, it was contralateral to the lesion in 59%, and ipsilateral in 29%, and the lesions were bilateral in 12%

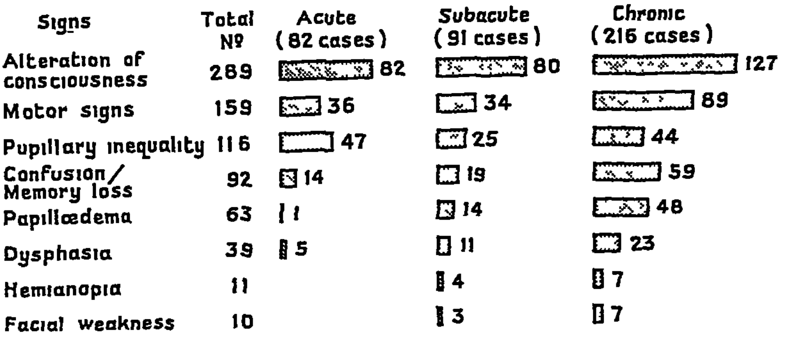

Fig 3—Frequency of neurological signs in the subgroups

Dysphasia, on the other hand, was always associated with a lesion of the dominant hemisphere Though homonymous visual-field defects were uncommon, they were not rare, and they had accurate lateralising value

Papillœdema was not uncommon in the chronic lesions, even when the pressure at lumbar puncture was normal or low This was also noted by Dressler and Albrecht (1957)

Though striking fluctuations in consciousness were not commonly recorded, this sign is a useful diagnostic pointer

Fig 3 does not include bradycardia, which was variable, nor the difference in percussion note over the vault, which was inconsistent, although stony dullness on percussion was often quite an accurate lateralising sign

Investigations

Lumbar Puncture

Lumbar puncture was performed preoperatively in only 120 cases The findings are set out in table II

The protein value, in only 42 cases, was below 50 mg per 100 ml in 27 cases and higher than this in 15, once being 130 mg Many conclusions cannot be drawn from so few lumbar punctures, but we can say that chronic lesions may be associated with normal or low pressure—a fact which may be important when considered with the clinical picture In view of the risks attending lumbar puncture in patients with space-occupying lesions, this investigation may often be omitted

TABLE II—FINDINGS AT LUMBAR PUNCTURE IN 120 CASES OF SUBDURAL HÆMATOMA

Subgroup	Acute	Subacute	Chronic	Total
No of lumbar punctures	6	28	86	120
Pressure over 200 mm	5	14	25	44
100–200 mm	1		38	39
below 100 mm.			23	23
not recorded		14		14
C S F xanthochromic	1	10	22	33
clear		6	64	70
bloodstained	5	12	0	17

Radiology

In some patients plain radiographs of the skull were not taken because the clinical state demanded urgent surgical intervention The findings were

	Acute	*Subacute*	*Chronic*	*Total*
Fracture only	28 (*14*)	17 (*3*)	12 (*1*)	57 (*18*)
Pineal displacement only	4 (*2*)	21 (*3*)	45 (*2*)	70 (*7*)
Fracture + pineal displacement	6 (*4*)	2 (*0*)		8 (*4*)
Pineal in midline	3 (*1*)	2 (*0*)	7 (*0*)	12 (*1*)
No abnormality	24 (*10*)	43 (*8*)	117 (*8*)	184 (*26*)
Plain films omitted	20 (*14*)	10 (*4*)	20 (*2*)	50 (*20*)

(Deaths in parentheses)

As would be expected, the incidence of fracture is higher in the acute group, indicating that more severe trauma is associated with earlier appearance of symptoms

Pineal displacement was usually associated with volumes of over 50 ml in the subdural space, but midline pineal glands were found in some unilateral cases with volumes of over 100 ml, and once with 200 ml Thus, though the number of cases is small, pineal displacement does not seem to be a significant prognostic factor, despite its diagnostic value

Angiography was performed in only 21 patients, in all of whom the correct diagnosis was made, only one died afterwards, but from unrelated causes The value of angiography as a safe, diagnostic method obviously cannot be assessed on so few cases, particularly as it was used only in patients in a reasonable clinical state, in whom an alternative diagnosis of vascular occlusion was possible Increasing experience with angiography in acute head injuries may in time point to whether one should use this technique rather than diagnostic burr-holes occasionally aided by ventriculography

The incidence of bilateral lesions in our series was

	Unilateral	*Bilateral*
Acute	55 (*67%*)	27 (*33%*)
Subacute	73 (*73%*)	18 (*20%*)
Chronic	178 (*84%*)	34 (*16%*)

The steady decrease in the frequency of bilateral lesions with increasing chronicity probably supports the suggestion that many small hæmatomas can be absorbed spontaneously (Browder 1943) Surgically it reaffirms the need for bilateral exploration.

Treatment and Results

Whilst the problems of surgical investigation and treatment are somewhat different in the three groups, we think that, retrospectively, they can be considered together The details are shown in table III

TABLE III—SURGICAL MANAGEMENT OF THE 389 CASES OF SUBDURAL HÆMATOMA

Subgroup	Acute	Subacute	Chronic	Total
Burr-hole exploration	77	91	200	368
Lesion found by burr-holes	66	89	184	339
Ventriculography required	11	2	16	29
Burr-holes and immediate craniotomy	10 - (*5*)	3 (*1*)		13 (*6*)
Burr-holes and delayed craniotomy	5 (*3*)	9 (*2*)	16 (*1*)	30 (*6*)
Burr-hole evacuation alone	62 (*31*)	79 (*15*)	184 (*11*)	325 (*57*)
Primary craniotomy			12 (*1*)	12 (*1*)
Died before surgery	5			5
No operation required			4 (calcified)	4

(Deaths in parentheses)

Acute and Subacute Cases

Our routine procedure is to make a burr-hole in relation to a fracture if present, but otherwise to make burr-holes bilaterally in the postparietal region If a liquid lesion is revealed it is evacuated, but if the lesion is solid, a craniotomy is likely to be necessary When burr-hole exploration does not reveal a significant lesion, the lesion is located by air studies

Our experience points to the source of bleeding being from the veins in relation to the sphenoid ridge or petrosal sinus in many cases, as suggested by Chambers (1951) But we were unable to correlate the site of the lesion with the direction of injury as did Bisgaard-Frantzen and Dalby (1957), admitting that in a retrospective study the relevant information is sometimes lacking

Though our figures do not support the view that immediate craniotomy is the treatment of choice in acute lesions, in our series craniotomy was adopted only in the more seriously affected patients Moreover, in some of the fatal cases which underwent burr-hole aspiration alone the lesion was inadequately treated by this technique In others, accessible associated traumatic intracerebral hæmatomas were discovered post mortem Our experience does suggest, however, that procedures such as subtemporal decompression are of no value and, by increasing venous congestion, may indeed be harmful (Aronson and Kaplan 1957)

Chronic Cases

21 of the chronic cases were diagnosed by angiography, and these were all later treated by burr-hole aspiration In the majority of chronic cases the lesion was suspected on clinical grounds and revealed by diagnostic burr-holes In many of these patients an expanding intracranial process was diagnosed, and the true nature of the lesion was revealed by burr-holes made before ventriculography But in some of them the lesion was revealed only by air studies, as, for example, in the 12 with ventriculographic findings suggestive of tumour in whom primary craniotomy was performed Craniotomy was performed after burr-hole drainage in the others if their condition deteriorated or if the lesion failed to resolve after repeated tapping of the subdural space

Associated Lesions

When considering surgical management one must not forget the possibility of associated lesions, for a significant subdural hæmatoma does not exclude or necessarily diminish the role they may play in the final outcome In our series they were

	Acute	*Subacute*	*Chronic*
Extradural hæmorrhage (unrecognised)	1 (*1*)		
Intracerebral hæmatoma	11 (*10*)	3 (*1*)	
Posterior-fossa hæmatoma	2 (*1*)		

The patient with an extradural hæmorrhage had a large subdural lesion, the extradural hæmatoma being contralateral to it The intracerebral hæmatomas were mainly found in the temporal region, and all these patients deteriorated after burr-hole evacuation of their subdural lesions In the acute group an intracerebral hæmatoma was in fact the commonest cause of immediate deterioration after evacuation of the subdural hæmatoma, only 1 patient in this group survived, and he had a stormy course When this patient died seven years later from lung cancer, necropsy revealed evidence of an old temporal-lobe hæmatoma 1 patient with a posterior-fossa lesion died soon after evacuation of the supratentorial hæmatoma, whilst in the 2nd the diagnosis was made later at ventriculography

Complications

The commonest " complication " of surgery was failure to improve after treatment, and these cases showed post-mortem evidence of gross cerebral œdema, brain-stem distortion, or frank hæmorrhage But we must consider further those cases which initially improved after surgery and later regressed, or in which surgery seemed to be deleterious These are shown in table IV

Epilepsy in the immediate postoperative period was usually in patients who had presented with this symptom, and, despite energetic measures for its control, a proportion of them developed intractable status epilepticus and died

Pneumonia was not purely a terminal illness, but in the elderly it was associated with general drowsiness The cases in which it supervened in the course of prolonged coma have not been included In recent cases respiratory complications have been more successfully managed by early tracheostomy, thus allowing of adequate bronchial toilet.

As previously mentioned, deterioration in the acute and subacute group after burr-hole evacuation was most commonly associated with intracerebral hæmatomas In some, however, it was due to inadequate removal of the lesion, and

TABLE IV—MODES OF DETERIORATION AFTER SURGERY

—	Acute	Subacute	Chronic	Total
Epilepsy	6 (*4*)	4 (*4*)	8 (*0*)	18 (*8*)
Pneumonia	6 (*6*)	4 (*4*)	5 (*3*)	15 (*13*)
Deterioration after burr-hole evacuation	17 (*15*)	2 (*1*)	6 (*1*)	25 (*17*)
Deterioration after craniotomy	2 (*2*)		3 (*2*)	5 (*4*)
Low-pressure syndrome	3 (*1*)	5 (*1*)	7 (*2*)	15 (*4*)
Further bleeding	1 (*1*)		4 (*1*)	5 (*2*)

(Deaths in parentheses)

in 3 cases it seemed to be part of the natural progression of the illness In the chronic group the patients were all elderly and with depression of consciousness Deterioration seemed to be associated with the sudden evacuation of a large lesion, for, in the case that died, when 100 ml of fluid had been removed, the patient suddenly became comatose, and necropsy later showed a large brain-stem hæmorrhage which presumably happened when the hæmatoma was evacuated Of the patients who deteriorated after craniotomy, the 2 acute cases showed gross cerebral œdema, and the 3 chronic cases showed hemisphere collapse, as reported by Pecker (1957), only 1 responding to treatment

Intracranial hypotension, as described by Knebs et al (1937) and Morice (1944), was present in 15 cases In all of them it was diagnosed by lumbar puncture, and all were treated by intrathecal injection of sterile normal saline and adequate general hydration 11 of these patients responded dramatically, though several required repeated intrathecal injections Cortisone, as suggested by Pecker (1957), was not used, neither did we adopt the technique of intravenous injection of distilled water (Holmes 1953)

State of Consciousness

The level of consciousness has a direct bearing on mortality in head injuries (Rowbotham et al 1954) and in spontaneous intracerebral hæmorrhage (McKissock et al 1959) In this series the state of consciousness on admission was studied with the following results

	Acute	*Subacute*	*Chronic*
Alert	0	11 (*0*)	89 (*2*)
Drowsy	22 (*8*)	58 (*10*)	80 (*6*)
Stuporose	35 (*18*)	12 (*4*)	35 (*4*)
Comatose	25 (*18*)	10 (*4*)	4 (*1*)

(Deaths in parentheses)

Patients were classified as alert if in spontaneous contact with their surroundings, regardless of dysphasia, drowsy if they could only be roused by stimulation, stuporose if inaccessible but able to respond in a purposeful manner to noxious stimulation, and comatose if without response to pain It is at once obvious that in all groups an increasing mortality is related to diminishing consciousness, but that the mortality is also related to the acuteness of the lesions Thus a patient who is drowsy with an acute lesion may have a worse prognosis than a stuporose patient with a chronic lesion

Size of Hæmatomas

The volume of the lesions seemed to bear no relation to prognosis

Outcome of Surgical Treatment

Table v shows the immediate surgical death-rates The overall mortality-rate was about 20%, but this figure is of limited significance as it obviously depends on the relative proportion in each group What is important is the good prognosis for the survivors, and this is most obvious in the subacute and chronic cases

TABLE V—OUTCOME OF CASES TREATED SURGICALLY

Subgroup	Acute	Subacute	Chronic
Total cases	77	91	212
Died after surgery	39	23	13
Died later from other causes	3	4	8
Lost in follow-up	3	5	12
Known survivors	32	59	179
Totally disabled	3	1	6
Partially disabled	11	5	23
Well	18	53	150
Surgical mortality-rate	51%	24%	6%

Discussion

Subdural hæmatoma can often be diagnosed with a fair degree of accuracy in patients with a history of recent trauma In such patients the indications for exploratory burr-holes or other investigations are quite definite In nearly 40% of cases, however, such a history is not forthcoming, and in these patients diagnostic errors are most likely to be made, many being elderly, with lesions of the chronic type One must remember that headache and mental symptoms, associated with few signs in the limbs, are prominent features in such patients, and may be attributed to atherosclerotic degeneration or cerebral thrombosis Particularly when dealing with elderly patients, the possibility of a subdural hæmatoma should not be overlooked, and the appropriate investigations must be made An untreatable lesion should never be diagnosed on clinical grounds alone Simple investigations, such as skull radiography, may be helpful in revealing a fracture, a displaced pineal gland, or signs of raised intracranial pressure Almost half our series showed such abnormalities At the same time completely normal findings—and even a midline pineal gland—do not exclude a subdural lesion Even the time-honoured investigation of lumbar puncture is usually unhelpful

The more elective investigations have to be considered against the background of presentation One cannot debate their relative merits in subdural hæmatoma, as the diagnosis is so often established when burr-holes are made for ventriculography In acute cases and others associated with known trauma the diagnosis of intracranial hæmatoma is often made In such cases the diagnosis is best confirmed or excluded by exploratory burr-holes, provided that if a significant lesion is not discovered ventriculography should be undertaken We have no firm views on the merits of angiography or ventriculography, and the decision must obviously depend on individual experience and the case concerned But if a subdural lesion is suspected in an elderly patient exploratory burr-holes are undoubtedly the investigation of choice, for this usually produces diagnosis and cure simultaneously

This study of subdural hæmatomas has demonstrated some of the diagnostic difficulties as well as some pointers to diagnosis Further views on prognosis have also emerged One of the most important is the significance of the level of consciousness at the time of treatment This emphasises the need for early diagnosis or suspicion of the lesion, before the patient's conscious state has regressed irreversibly Of equal importance is the chronicity of the lesion, in that the more rapidly the symptoms evolve the worse the prognosis, as shown by the different mortalities in the three groups (table I)

Associated injuries are always likely Many intracerebral hæmatomas were found in the acute group, and particularly in patients whose condition deteriorated after evacuation of the subdural collection, in whom a second space-occupying lesion was often found

Age clearly influences mortality Over seventy the older the patient the worse the prognosis, presumably because the ageing cerebrovascular state does not allow of such gross disturbances

The prognosis therefore rests mainly on the changes in the brain as a consequence of the hæmatoma, this being reflected in the state of consciousness and in the rate of evolution of the clinical picture, but the outcome is naturally worse if there is associated brain damage, and it is aggravated by increasing age

Summary

389 cases of proven subdural hæmatoma are presented They were subdivided into acute, subacute, and chronic varieties

The most important prognostic factors were the patient's state of consciousness at the time of treatment, and the rate of evolution of the clinical picture. Age also influenced prognosis, but factors such as the size of the lesion, the nature of the trauma, and hypertension, had limited significance

In acute and subacute cases burr-hole explorations were made in the first place, in chronic cases the lesion was usually suspected clinically and later revealed by burr-holes Craniotomy was adopted only in the more seriously affected patients

The common complications of surgery included failure to improve because of gross cerebral œdema, brain-stem distortion, or hæmorrhage, epilepsy, pneumonia, intracerebral hæmatoma, and intracranial hypotension

The total operative mortality-rate was about 20%, and of the 270 known survivors, 221 made good recoveries The need for early diagnosis and treatment has been stressed

We should like to thank the Wolfson Foundation for a grant to A R , which has helped to make this work possible

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MENTAL ABNORMALITIES FOLLOWING SUBDURAL HÆMATOMA *

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CHRONIC subdural hæmatoma is a common complication of less severe head injuries (Peet 1949) Trotter described the condition in 1914, but it was Putnam and Cushing (1925) who stimulated interest in it Even so, until fairly lately subdural hæmatomas were very often discovered only at necropsy The apparent notable increase in frequency of this condition is probably due to three main factors (1) the increased number of head injuries, (2) the increasing life expectancy (most patients with this condition are aged 40–70 [Peet 1949]), and (3) increased awareness of this complication.

Diagnosis

In subdural hæmatoma a head injury sometimes almost too trivial to be remembered usually precedes the onset of headaches, which may be generalised or localised. Symptoms of raised intracranial pressure, such as visual failure and vomiting, may occur, but more commonly headache is associated with fluctuation in the level of consciousness, sometimes with incontinence of urine Periods of apparent normality alternate with periods of drowsiness, which increase in duration as time passes In longstanding cases impairment of mental function may proceed to dementia

The physical signs may be few confusion, inattention, and apathy may be the only manifestations of bilateral lesions Focal signs may indicate a localised hæmatoma, and these differ in no respect from those of other space-occupying lesions Lumbar puncture may reveal a normal pressure and cerebrospinal fluid, and the arteriographic and pneumoencephalographic appearances are characteristic The electroencephalogram is sometimes of help, but the surest way of confirming the diagnosis is by making burr-holes

Treatment

In most cases the hæmatoma is easily evacuated by suitably placed burr-holes The fluid hæmatoma is aspirated and the subdural space carefully irrigated with saline solution, Ringer's solution, or an 0 5% solution of 'Milton' to dislodge any residual clots If the hæmatoma is solid with membrane formation, a formal osteoplastic flap is raised and the clot and membrane are removed

In the present series of 44 consecutive cases of head injury admitted to the neurosurgical unit there were 11 cases of chronic subdural hæmatoma Of these 11 patients 4 were cured and discharged from the unit to their homes, and 3 died in hospital at various times after operation, 4 were transferred with mental abnormality to a mental hospital, where 2 died after two months and the other 2 remain (see table)

All patients who died were examined post mortem, and it was confirmed that no other cerebral lesion could be held responsible for death In each case death was ascribed to bronchopneumonia

Discussion

This small series is necessarily selected The cases were, however, consecutive, all being admitted from other hospitals in the area served by the unit They represent a very small proportion of the total number of head injuries in the area served The high proportion of subdural hæmatomas in this series and the high mortality may be partly accounted for the large number of elderly retired people on the South Coast, and the consequent high average age of the patients

I have found no reported record of the mortality of a comparable series, but the incidence of mental disease following cerebral trauma seems to be relatively low

Of 70,987 cases of head injury, May (1949) found that mental disease developed in 0 3% Bowman and Blau (1949) found 192 cases of mental disease following trauma in a series of 25,269 Frazier and Ingham (1920) found 4 cases of mental disease in a series of 200 gunshot wounds of the head Earley (1935) found that of 100 cases of fractured skull, defective memory developed in 7, personality changes in 4, and traumatic psychosis in 3 Stone and Brams (1927) in a series of 54 severe head injuries found 3 cases of traumatic psychosis, while Glaser and Shafer (1932) found mental disease in 9% of 225 cases of head trauma.

Ætiological Factors

In the present series of 11 cases of subdural hæmatoma, the 4 patients in whom mental abnormalities developed were all males Of 192 cases mental disease described by Bowman and Blau (1949) in which mental disease developed, only 16 were females

Arteriosclerosis and alcoholism are the two main conditions predisposing to serious sequelæ following head injuries Most workers agree that the serious after-effects

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* Based on a paper read before the Society of British Neurological Surgeons, November, 1958

DATA ON 11 CASES OF SUBDURAL HÆMATOMA

Case no	Age (yr)	Sex	Interval from injury to operation (days)	Nature of operation	Operative findings	Mental state	Result	Cause of death
1	35	M	9	Burr-holes	Bilateral clot, partly fluid, partly solid	Personality disorder, delusions	Survived in mental hospital	
2	74	M	5	(1) Burr-holes (2) Osteoplastic flap	Rt-sided clot, partly fluid, partly solid, cortex did not expand	Dementia, aggressive hallucinations	Died in mental hospital 2 mos later	Collapse of lung and pneumonia
3	52	F	?	Burr-holes	Rt-sided clot, fluid	Confusion	Died 3 days later	Bronchopneumonia, no abnormality found in brain
4	62	F	11	Burr-holes, 2 aspirations	Rt-sided fluid hæmatoma	Confusion, then normal	Home, cured	
5	68	M	14	Burr-holes, 3 aspirations	Bilateral subdural hygroma, brain did not expand fully	Confusion, dementia	Mental hospital, died 2 mos later	Bronchopneumonia, no abnormality found in brain
6	67	F	6	Burr-holes	Lt-sided fluid hæmatoma, cortex did not expand	Normal	Home, cured	
7	72	F	?	Burr-holes	Bilateral hygroma	Coma	Died 4 days later	Bronchopneumonia, no abnormality found in brain
8	56	F	19	Burr-holes, fluid and air into ventricles	Cortex depressed, did not expand	Dementia	Died 3 mos later	Pneumonia
9	57	M	28	Osteoplastic flap and decompression	Partly fluid, partly solid, rt side	Normal	Home, cured	
10	58	M	16	Burr-holes, fluid injected into ventricles	Bilateral hygroma	Korsakow's syndrome	Mental hospital	
11	72	F	13	Burr-holes	Bilateral membrane present	Confusion which cleared in few weeks	Home, cured	

of head injury, such as mental abnormalities, are found mostly in older patients

Classification of Mental Disorders following Trauma

The following classification by Mayer-Gross et al (1954) is simple and adequate

Three main patterns of disturbance of mental function may follow trauma (1) clouding of consciousness, (2) dysmnesic syndrome (a defect of retention and all aspects of memory), (3) dementia

In the chronic stage which may follow subdural hæmatoma, the disabilities are classified as (1) organic defects ([a] post-traumatic dementia and personality change, [b] post-traumatic epilepsy and focal neurological syndromes), (2) functional-organic defects (postconcussional or post-contusional syndrome), (3) precipitated endogenous and organic psychosis

In the present series of 11 cases confusion was present in 7 in the early stages postoperatively and remained permanently in 4 Personality disorder was prominent in 1 case, and dementia was found in 3, aggressive hallucinations occurred in 1 patient with dementia In a patient aged 58 Korsakow's psychosis developed over a year after his hæmatoma had been evacuated, this patient is still under treatment in a mental hospital 2 patients had delusions

All the patients, except 1 who was comatose, appeared mentally normal before operation In all cases a unilateral or bilateral subdural hæmatoma was found, and the mental abnormalities occurred after the hæmatoma had been successfully evacuated In 3 cases the hæmatoma was partly solid and partly fluid In 4 cases the brain on one or other side did not expand after the hæmatoma had been evacuated This finding is of grave significance of these 4 patients 3 died, and only 1 recovered satisfactorily Lalonde and Gardner (1948) emphasised the seriousness of this finding, and recommended the injection of normal saline intrathecally by the lumbar route in all such cases, they claimed good results, and had also had a satisfactory outcome when the ventricles had been gently distended with saline This procedure was tried in 2 of the present cases, in 1 it was successful, and in the other it was not The reason why the brain does not expand is not fully understood, but vascular thrombosis superimposed on arteriosclerosis may be responsible

Treatment

The earlier the subdural hæmatoma is diagnosed and treated, the more likely is the result to be successful—though in case 9 of the present series, when operation was delayed for twenty-eight days, the patient recovered well and returned home cured

In elderly patients care of the chest is most important A suitable antibiotic is given, and the patient is turned from side to side every two hours if unconscious, but, if the patient is sufficiently alert, breathing exercises are given at regular intervals The skin is washed and rubbed with spirit, and powdered every four hours, and the bowels are regulated by aperients or enemas Incontinence of urine is often present, and in order to prevent bedsores it is necessary to drain the bladder by an indwelling polyethylene tube Tracheotomy is a life-saving procedure in patients who remain long unconscious Later treatment consists in mental and physical rehabilitation in the surroundings of a modern mental hospital

44 consecutive cases of head injury included 11 instances of subdural hæmatoma

4 patients recovered, 3 died in the neurosurgical unit, and 4 were admitted to a mental hospital, where 2 of these died, and 2 have remained mentally deranged

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UNSUSPECTED TREATABLE ORGANIC DEMENTIA

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PROGRESSIVE mental deterioration is often accepted as a psychiatric diagnosis, and the underlying cause may remain unrecognised. The purpose of this note is to underline the need for accepting such a diagnosis with the utmost caution, and we would stress the need for early investigation of these patients. The closer association of psychiatric diagnosis and treatment with general hospitals in the future should help in detecting organic disease in patients who would otherwise be regarded as having a psychopathic dementia. It is certain that in some of these patients the root cause has gone unsuspected to the grave.

The following are illustrative cases and do not exhaust our experience. Four of the five have presented in the past year.

Case-records

Case 1.—A lively healthy schoolboy of 13 was mentally normal until Christmas, 1958. Thereafter he became morally defective and inexplicably took to thieving; he had eight convictions for theft in three months. His parents could no longer control him and he was belligerent and aggressive. His stock remark to parents and magistrates was "Drop dead." This conduct secured him admission to a remand home where he disturbed the peace by crying and singing at night. He did complain of headaches "like hammering" and for two months vomited two or three times a day. He was repeatedly examined medically but no diagnosis other than "high temperature" was made. He was admitted to hospital for a few days but his conduct there resulted in early discharge. A temporary palsy of the left leg "responded well to slapping". In June he saw a psychiatrist who reported that "his behaviour is half-way between hysteria and malingering, but a cerebral tumour must be eliminated".

The officer in charge of the remand home, undeterred by the negative medical opinion, insisted that the boy was ill, and at last he was admitted to this hospital on Aug. 19, 1959. He had lost consciousness on the morning of admission and had bilateral papillœdema and hæmorrhages in the fundi but no localising signs. Carotid arteriography revealed a large right frontal space-occupying lesion. Exploration revealed a large right frontal cerebral abscess, which was drained by aspiration. Six weeks later he was discharged symptom-free and mentally normal. In his own words: "It took them a long time to find out what was the matter with me."

Case 2.—An elderly man of 77 had good health and occupied himself by hard work in his garden and with odd-jobbing for his neighbours. Just before Christmas, 1958, while digging round one of his apple trees he struck his head sharply on a branch. He felt momentarily dazed but soon recovered. Next day his right foot dragged, and when on his way home from a neighbour's he fell over. From then on he deteriorated mentally, becoming drowsy, incontinent, confused, and completely unlike his former self.

It was not until Jan. 26, 1959, that he was admitted to this hospital drowsy and confused and with a right facial weakness but no other localising sign. Carotid arteriography revealed a large right parietal subdural hæmatoma. After evacuation of this he progressed well and was discharged mentally recovered three months later without any paresis.

Case 3.—An epileptic woman of 60 sustained a fracture of the left parietal bone in 1954 during a fit. Thereafter she became confused and ataxic with nystagmus and dysarthria. In 1958 a subdural hæmatoma was suspected but cerebral arteriography failed to confirm this. Her fits continued and her intelligence deteriorated further. Her husband, who had looked after her devotedly, tried to strangle her but desisted and gave himself up to the police. The patient was temporarily admitted to another hospital and the husband was admitted to a mental hospital. Six months later the patient collapsed in the street and was brought into this hospital on May 7, 1959, with a left facial paresis and a large right pupil but no other localising signs. She was comatose, but the coma was only temporary. Carotid arteriography revealed a large right parietal hæmatoma. This was evacuated with much difficulty; it was clearly a chronic one, for the underlying cerebral cortex was atrophic. Her mental state did not improve.

Case 4.—A man of 58 lived by himself in a caravan. He developed pneumonia and was admitted to hospital with a lung abscess which responded to antibiotics, and he was discharged on Aug. 21, 1959. The same evening neighbours heard him making a noise and he was later found confused and incontinent. He refused to see a doctor, but the police later brought a doctor to see him. He was readmitted five days later to the same hospital, where his condition continued to deteriorate. By Sept. 3, 1959, he was deeply unconscious and incontinent with a left hemiparesis. He was then transferred to this hospital. Carotid arteriography showed a large right parietal subdural hæmatoma. This was evacuated and his mental state was normal the following day. He was discharged twelve days later.

Case 5.—A nun of 41 was returning to her convent in London from a visit to her relations in Dublin. She arrived at Euston station in an extremely drowsy state, having entered the train herself at Holyhead. She was removed from the train and taken to the convent by ambulance. When seen by a doctor next morning she was fully conscious, and though voluble appeared to be otherwise normal. She remembered her arrival at Euston station but did not know how she had got to the convent. Later in the morning she lapsed into semicoma but still without any localising sign. From subsequent inquiry it appeared that she had been increasingly forgetful and unable to concentrate for at least six months. She was slow to get up in the morning, and it took an hour or two for her to "wake up". She had had occasional headaches and had vomited at times. She was admitted the same day to this hospital in semicoma; her left pupil was dilated but there were no other localising signs. Carotid arteriography revealed a deeply situated right temporal meningioma. This was removed successfully, and the patient was discharged five weeks later symptom-free.

Comment

It is very easy to ascribe changes in the psyche to mental deterioration in the elderly, to the effects of prolonged epilepsy in those subject to that disease, to dementia præcox in the young adult, and to moral deficiency in the youngster, when in fact a very real organic intracranial cause is directly responsible. Many a treatable patient must have been buried with the wrong diagnosis on the death certificate. The examples we have instanced are not exceptional: they illustrate a cautionary tale.

We wish to acknowledge assistance given by our clinical colleagues, especially Mr. T. G. I. James, in allowing us access to their records.

"Even the governments have neglected unduly the larger considerations in their stress upon disarmament as a precondition for large-scale assistance, for unless greater stability is achieved in the areas of social ferment, the temptations and dangers of such instability will tend to undermine the conditions for disarmament. Indeed, they pose a major threat to an all-too-fragile peace."—RICHARD M. FAGLEY, *The Population Explosion and Christian Responsibility*. New York, 1960.

A SURGICAL APPROACH TO THE MANAGEMENT OF HEART-BLOCK

USING AN INDUCTIVE COUPLED ARTIFICIAL CARDIAC PACEMAKER

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Complete heart-block may be symptomless, disabling because of low cardiac output, or a threat to life because of repeated Stokes-Adams seizures Medical treatment is unsatisfactory

When life is threatened by repeated Stokes-Adams seizures, artificial pacemaking is indicated Success has been achieved by external pacemaking (Zoll 1952, Zoll et al 1954, Leatham et al 1956) and by the use of a cardiac electrode passed into the right ventricle from the arm (Furman and Robinson 1958) The first method causes painful muscle contractions with each stimulus, while the second may lead to venous thrombosis (despite anticoagulant therapy) and even to perforation of the heart These methods are therefore temporary

The occurrence of complete heart-block after repair of ventricular septal defect has provided a stimulus to a surgical approach Lillehei (Weirich et al 1957) showed that such heart-block could be treated successfully with suture electrodes in the ventricular muscle, brought out through the chest wall to a pacemaker We have applied this technique to the treatment of recurrent Stokes-Adams seizures in non-surgical acquired heart-block The leads through the skin make this method unsuitable for permanent use

There are patients in complete heart-block without Stokes-Adams seizures who are disabled by low cardiac output The fixed bradycardia of idioventricular rhythm permits an increase in cardiac output only by an increase in stroke volume of the heart, which may be limited by varying degrees of myocardial damage An artificial increase in pulse-rate should enable such patients to increase their cardiac output It would be desirable to treat these patients by artificial cardiac pacemaking if the disadvantages of the methods described could be overcome

We have developed an inductive coupled cardiac pacemaker which gives painless control of the heart-rate through the intact skin This instrument consists of a primary and secondary circuit (fig 1) The secondary circuit consists of a nylon-embedded induction coil fixed in the left pectoral muscle over the second intercostal space at thoracotomy (fig 2) The ends of the coil are continued as nylon-covered braided stainless steel wires, with atraumatic needles on the bare ends, which are fixed in the ventricular muscle The needles are then removed When the wound is closed the coil forms an easily palpable tumour which is not tender

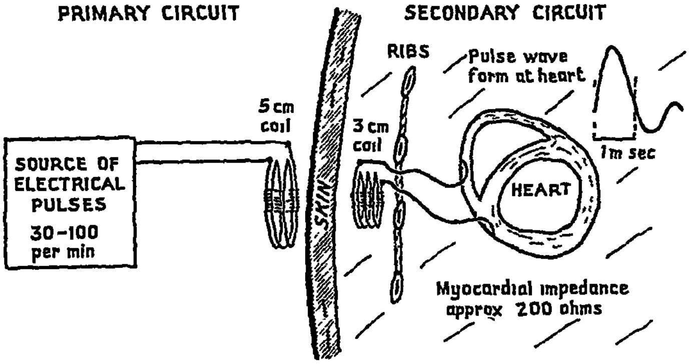

Fig 1—Diagram of the method of inductive coupled pacemaking

The primary circuit consists of an inducing coil supplied by a portable transistor pulse generator which produces short pulses at adjustable intervals and intensity (fig 3) The primary coil is fixed to the skin over the secondary coil in which the pacemaking pulse is induced

We report control of the heart-rate of three patients by this method

Case-records

THE FIRST CASE

A woman of 56, a secretary, was well until last October, when she had two episodes of sudden loss of consciousness, each lasting about half a minute No convulsions were observed For the next 3 months she had momentary attacks of giddiness several times a day, especially on changing posture, and had two episodes of sudden transient loss of consciousness She

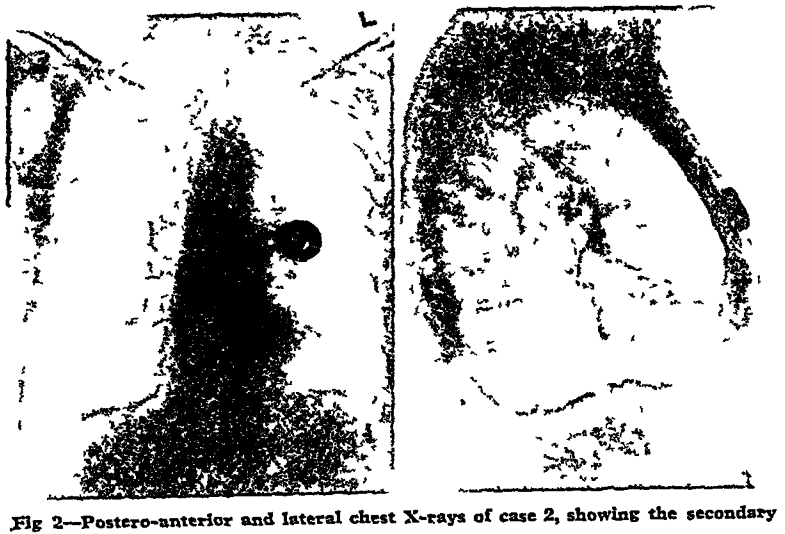

Fig 2—Postero-anterior and lateral chest X-rays of case 2, showing the secondary coil in place

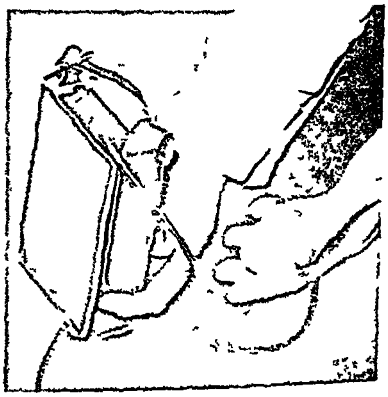

Fig 3—The transistor pulse generator and the inducing coil.

was admitted to another hospital on Jan 21, 1960, after having two further episodes of loss of consciousness, at work, each lasting about 3 minutes. Complete heart-block with Stokes-Adams seizures was diagnosed. The pulse-rate was 29 and the electrocardiogram showed atrioventricular dissociation.

Treated with ephedrine and 'Hyperduric' adrenaline, she had no further seizures until February 11. During the following 36 hours she had five Stokes-Adams seizures in which cardiac asystole was observed. The two most severe caused unconsciousness for 4 minutes and she became temporarily maniacal on recovery. She was then transferred to this hospital.

On examination here she was intelligent and cooperative. She was in mild congestive cardiac failure with a left pleural effusion. The pulse was regular (rate 28) and her blood-pressure was 170/60 mm Hg. The heart was not enlarged. The heart sounds were normal and there were no murmurs, but there were occasional ectopic beats which did not achieve ejection.

It was thought that urgent cardiac pacemaking was indicated and thoracotomy for insertion of myocardial electrodes was advised. In view of the possibility that after a period of pacemaking by Lillehei's method Stokes-Adams seizures might cease, it was decided to insert the secondary coil of the inductive coupled pacemaker at the same time.

Immediately before induction of anæsthesia she had another Stokes-Adams seizure. After $1^1/_2$ minutes' asystole a needle was inserted through the left 4th interspace into the heart and a second into the skin. These were attached to a pacemaker and pacemaking was established at a rate of 80 per minute. She recovered consciousness but became maniacal, making induction of anæsthesia difficult. After this was achieved she again became pulseless, and a rapid left anterior thoracotomy was performed which revealed cardiac tamponade. The pericardium was full of blood from the needle puncture in the right ventricle. The heart was flaccid and arrested but responded immediately to massage at an idioventricular rate of 48. A blood-transfusion was given into the right ventricle while massage was continued. The heart-beat became more vigorous and its rate was increased to 90 by application of the pacemaker. The episode of asystole and hypotension lasted about 4 minutes. Removable nylon-covered stainless-steel wire electrodes were attached to the right and left ventricles and brought out together through the chest wall below the incision. Pacemaking was continued through these. The secondary coil and its leads were then fixed and the chest closed.

After the operation she was comatose and spastic with athetoid movements of the limbs and bilateral extensor plantar responses. Her breathing was stertorous and there was excessive bronchial secretion. A tracheostomy was performed. The blood-pressure was 120/80 mm Hg. 8 hours later she was still comatose but the spasticity was less, and after 14 hours she recovered consciousness. Her progress was slow but her cardiovascular state was satisfactory on the pacemaker at 80 with a blood-pressure of 120/70 mm Hg and resolution of heart-failure in 48 hours. At this stage she had retrograde amnesia of 1 month which has since resolved. Now the only evidence of neurological damage is slight word-finding difficulty.

For the first 2 months after operation, although idioventricular rhythm started as soon as the pacemaker was switched off she lost consciousness almost immediately and pacemaking by the Lillehei method was therefore continued. It was also found possible to control the heart-rate through the inductive coupling. After 8 weeks she no longer became unconscious when the pacemaker was turned off, but felt faint and apprehensive and became pale, the pulse-rate was 22. At that time she was walking about the ward and going home for the day with her pacemaker. After 3 months it was noted that when the pacemaker was switched off she remained conscious and did not suffer faintness for periods of an hour at her idioventricular rate of 24. Control with the inductively coupled pacemaker has been achieved at every attempt and she can now apply it herself.

THE SECOND CASE

A factory supervisor, aged 60, underwent prostatectomy for benign hypertrophy in October, 1958, at which time his pulse-rate was 88 and no cardiovascular abnormality was noted. He was well until 6 days before transfer to this hospital, on April 14, 1960, when, in the afternoon, he had a series of attacks during which he felt a hot flush spreading from the chest to the temples, associated with a throbbing in the head, and a sensation of jerking movement of his arms, which he knew were still.

During the next 4 days he had several such attacks culminating in one which began as the others, but in which he lost consciousness. His wife observed that his eyes became glazed, he dropped his cup and slumped forward in his chair. His own doctor was called and observed a further such attack during which he was pulseless for 30 seconds and on recovery had an irregular pulse. He was admitted to another hospital that evening, by which time eighteen further attacks had occurred. He had a regular pulse of 88 with periods of absent pulse lasting 4–5 seconds not associated with symptoms. A diagnosis of Stokes-Adams seizures was made.

An electrocardiogram next morning showed an atrial rate of 100 and periods of grade-I heart-block with a PR interval of 0·2 second, the Wenckebach phenomenon, 3-to-1 heart-block, and periods of ventricular asystole. He was treated with ephedrine but his attacks continued and he was transferred here 48 hours later.

On examination he was alert and cooperative. His pulse was regular (rate 108) and his blood-pressure was 120/90 mm Hg. The heart was not enlarged, the sounds were normal and there were no murmurs. He had chronic bronchitis and emphysema. There was no evidence of cardiac failure. During examination he said "I'm going" and lost consciousness. A period of asystole lasting 30 seconds was observed. A regular pulse returned at a rate of 65 and was associated with reactive hyperæmia. It was decided to pass a cardiac catheter electrode for pacemaking and he was heparinised. The catheter electrode could not be made to enter the right ventricle. Two further Stokes-Adams seizures occurred, so immediate thoracotomy and insertion of pacemaker electrodes was performed. A secondary coil was also inserted.

He had no further attacks while on the pacemaker at a rate of 85. Next day the pacemaker rate was reduced to 70 and the pulse was observed to become irregular owing to interference by the natural sino-auricular pacemaker. When the pacemaker was switched off, sinus rhythm (rate 80) with periods of asystole causing faintness, was observed. It was found that when the artificial pacemaker rate was reduced to 60 no interference with the natural rhythm occurred but asystole was prevented, being replaced by periods of pacemaker control. No further Stokes-Adams seizures occurred on this regime. After a week the pacemaker was switched off during the day and the patient switched it on at the onset of faintness and whenever he wanted to sleep. After 2 weeks the attacks ceased but he continued to use the pacemaker at night. A week later pacemaking was stopped and he remained in sinus rhythm. The percutaneous electrodes were removed.

During the postoperative period repeated trials of the inductive coupled pacemaker were made. Increase of the heart-rate was always achieved and the patient has learned to apply it himself.

THE THIRD CASE

A man of 66, an engineering representative had suffered from chronic bronchitis since childhood. 5 years ago he became breathless on effort, 4 years ago a diagnosis of hypertensive heart-disease was made and he was digitalised. Last December his breathlessness on effort increased and he became orthopnœic. He developed congestive cardiac failure which responded temporarily to diuretics. At that time he had a slow pulse and an electrocardiogram showed 2-to-1 heart-block.

He was admitted to another hospital on April 6 in severe congestive cardiac failure. His pulse was regular (rate 32) and his blood-pressure was 210/90 mm Hg. The heart was enlarged and there was an apical systolic murmur conducted to the axilla. On April 7 an electrocardiogram showed complete heart-block with an idioventricular rate of 35. His mental state was dull and his manner aggressive. There was no history suggesting Stokes-Adams seizures. There was some response to chlorothiazide, and, when he was transferred to this hospital, his cardiac failure was resolving.

It was thought that he might benefit from artificial cardiac pacemaking and he was given phenindione preparatory to a study of his cardiac output during pacemaking. On April 14 a cardiac-catheter electrode was passed from the right arm to the right ventricle. Pacemaking was achieved at 0·5 volts. A double-lumen cardiac catheter was passed from the left arm so that simultaneous pulmonary-artery and pulmonary-wedge pressures could be recorded. A needle was inserted in the right brachial artery. Direct Fick cardiac outputs were measured at his idioventricular rate of 30 and at pacemaker rates of 51, 72, and 95 (fig. 4). At a pacemaker rate of 72, coincidental with a rise in cardiac output and a drop in pulmonary-arterial and pulmonary-wedge pressures, the patient had striking relief of tightness in the chest and his orthopnœa ceased.

In view of these findings cardiac pacemaking with the intracardiac electrode was continued at 72. The next morning the patient was lucid, cooperative, and pleasant in manner. 4 days later, the pacemaker became ineffective and he had developed basilic-vein thrombosis, although his anticoagulant therapy was apparently adequate. He had an idioventricular rate of 46. The next day thoracotomy for insertion of pacemaking electrodes and a secondary coil was carried out. When the pericardium was opened the fluid was brown and 15 cm. of cardiac catheter was found protruding through the wall of the right ventricle. When the catheter was removed there was no bleeding from the heart.

After the operation, pacemaking by Lillehei's method was continued at a rate of 72. The inductive coupled pacemaker also controlled his heart satisfactorily. His heart-failure has now resolved and he is getting up. His breathlessness is less than at any time since last December. When his pacemaker is switched off he now develops idioventricular rhythm immediately (fig. 5), at a rate of 42, without faintness, breathlessness returns after 2 hours of idioventricular rhythm and is relieved by pacemaking. He is now using his inductive coupled pacemaker as a cardiac aid and is not breathless walking about the ward.

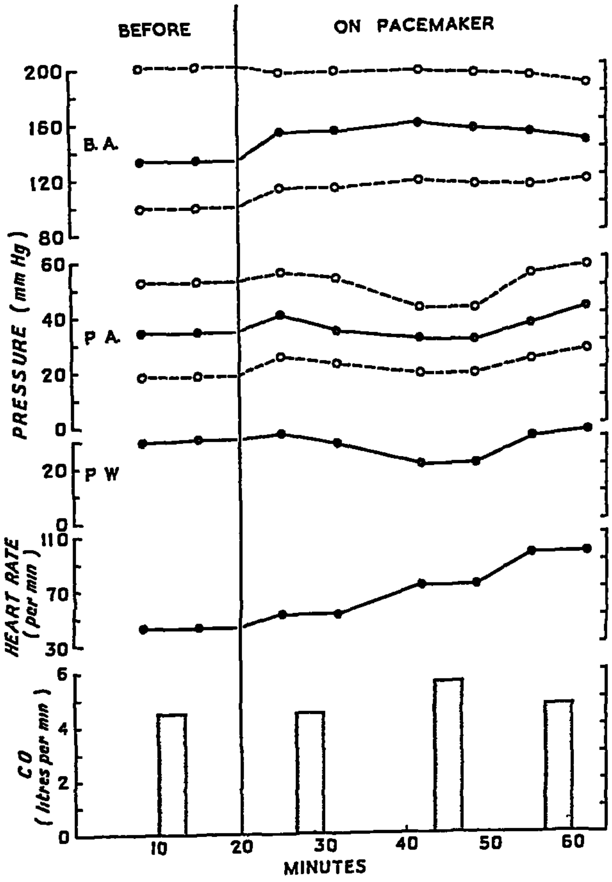

Fig. 4—Cardiac catheter findings in case 3.

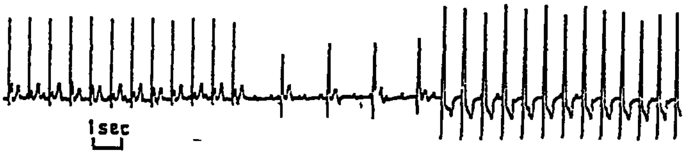

Fig. 5—Continuous electrocardiographic record in case 3 showing, from left to right, Lillehei pacemaking, idioventricular rhythm, and inductive pacemaking (the biphasic pulse is seen). Idioventricular rhythm occurs immediately after switching off the pacemaker.

Discussion

Artificial cardiac pacemaking by Lillehei's method seems to be indicated for Stokes-Adams seizures which threaten life. After a period of pacemaking, patients with this disease may revert to sinus rhythm or develop idioventricular rhythm without episodes of asystole. In either case there is a likelihood of further Stokes-Adams seizures and in the latter the cardiac output may be low. Artificial cardiac pacemaking by means of permanent percutaneous electrodes is undesirable. The method presented here overcomes this disadvantage and those of the other methods mentioned. It has the advantage that pacemaking is optional and that the rate and intensity of the electrical pulse is controllable. There are reports that the voltage necessary for pacemaking increases with time, owing to polarisation of the electrodes. None of our patients has required an increase of voltage since operation, but the longest period is only 4 months. The biphasic form of the pulse produced by the inductive coupling may help to minimise polarisation. The advantages of this method make it suitable for use as a safeguard against further Stokes-Adams seizures or as a cardiac aid for the correction of low output due to idioventricular rhythm. We hope that improvements in technique will make this method suitable for permanent pacemaking. P-wave control of the rate of a cardiac pacemaker has been achieved (Folkman and Watkins 1957). We intend to apply this physiologically desirable refinement to inductive coupled pacemaking.

Summary

The treatment of heart-block by artificial cardiac pacemaking is discussed. Three cases are reported. Two of these suffered repeated Stokes-Adams seizures threatening life. The third had low cardiac output due to idioventricular rhythm.

Their successful treatment by artificial cardiac pacemaking is described and a method of painless artificial cardiac pacemaking through the intact skin is presented.

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PNEUMONIA WITH ANTIBODIES TO STREPTOCOCCUS MG

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SINCE the late '30s clinicians have been interested in atypical pneumonia This is usually a benign disease for which no bacterial cause can be found, it does not respond to chemotherapy or treatment with antibiotics The increase in knowledge of the disease has been ætiological rickettsiæ, as in Q fever, and viruses, such as the adenovirus, have been associated with atypical pneumonia There remains a group of pneumonias of obscure ætiology, in many ways similar to known viral infections

The search for the cause of atypical pneumonia began with the isolation of a virus from cases of the disease by Eaton et al (1944) Liu (1957) claimed to have isolated a virus in the developing chick embryo, this virus was antigenically similar to Eaton's virus Cook et al (1960) refer, not to " Eaton's virus ", but to " Eaton agent "

Cook et al showed a fairly constant relationship between pneumonia associated with cold-agglutinins or *Streptococcus* MG antibodies and the presence of Eaton agent They infer that Eaton agent is a cause of atypical pneumonia, the finding of cold-agglutinins and *Streptococcus* MG antibodies are both non-specific In general practice, the study of atypical pneumonia must depend on the finding of *Streptococcus* MG antibodies, as the testing for cold-agglutinins presents technical hazards which are difficult to overcome

Cook et al (1960) subdivided cases of primary atypical pneumonia into those with negative serology and those that are cold-agglutinin-positive or *Streptococcus*-MG-positive. The 20 cases described here fall into the latter group, for brevity they will be described as cases of *Streptococcus* MG pneumonia, without intending to infer that the *Streptococcus* MG is the cause of the disease

Illustrative Case-records

Case 18 —An unmarried female veterinary assistant, aged 36, had pulmonary tuberculosis in 1948 when she was a hospital nurse, she was treated for 6 years by a right artificial pneumothorax and the disease had remained inactive On Sept 29, 1958, she felt slight malaise, limb pains, and slight frontal headache, and had several rigors She was pyrexial and went to bed On the 3rd day of illness she noted pain in her left chest, unaffected by respiration but worse if she lay on her left side

The patient, examined at home on the 4th day of illness, had a temperature of 100 2°F, pulse-rate 100 per minute, and respiration-rate 20 per minute She was pale but not cyanosed, the conjunctivæ, nasopharynx, and cervical glands were clinically normal The chest was normal, though the left base moved less than the right Symptomatic treatment only was given

On the 5th day her pain had gone and she felt better, she started to cough without sputum, but she had no rigors A few râles were heard at the right base After that her condition deteriorated, her temperature was 99–100 °F but rose to 102°F with rigors, of which she had several each day The cough and headache increased gradually, there were only small amounts of mucoid sputum On the 8th day the right lung base was dull to percussion, the breath sounds were diminished, and scattered râles and inspiratory crepitations were heard These signs increased in extent until the 10th day when she was examined by a chest physician, who reported patchy opacity in the left lower zone in the chest radiograph Tetracycline, 250 mg q d s, was given for the next 5 days, her symptoms, notably the cough, decreased and she was allowed up for short periods On the 17th day a chest radiograph showed no diminution in the shadow in the left lower zone, the chest physician recommended further tetracycline, which was given as before for 5 days (total dose 10 g)

Recovery was not complete until the 4th week, and the patient returned to work 35 days after the onset She relapsed immediately with influenza-like symptoms and slight soreness of the throat That evening her temperature was 100 2°F, she had granular pharyngitis and moist sounds at both bases Nose and throat swabs were taken and benzylpenicillin 2,000,000 units were given by intramuscular injection, 1,000,000 units were given twice daily for the next 4 days (total dose 10 million units) 8 weeks from the onset of the original illness she was clinically and radiologically normal and she returned to work. Since then she has remained in normal health

Laboratory Findings

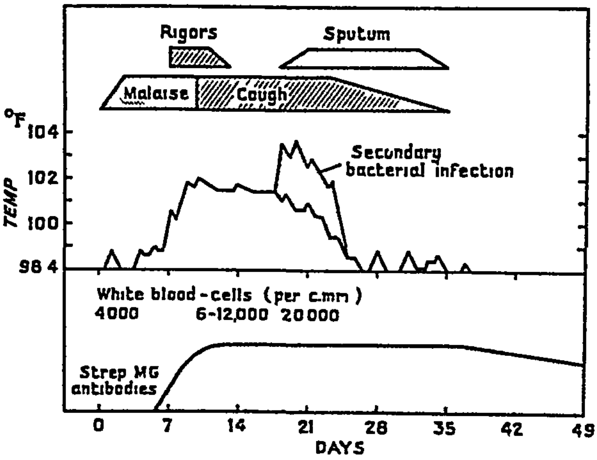
Nose and throat swabs (4th and 36th day) did not reveal any pathogens Sputum (10th day) showed a scanty growth of normal upper-respiratory organisms Blood examination (4th day) hæmoglobin 12 7 g per 100 ml , red-cell count normal, white cells 6800 per c mm , differential count normal

Serum taken on the 4th, 14th, 22nd, and 34th days of the illness agglutinated *Streptococcus* MG at these dilutions <10, <10, 10, 40

Case 19.—A housewife, aged 32, with no significant past history, on Jan. 14, 1959, felt a dull pain in the back and was shivery, there was no coryza or sore throat On the 4th day of illness she started to cough, without sputum at first but later raising about one ounce daily of colourless sputum During this 1st week the shivering and back pain persisted and there was increasing malaise She sweated heavily at nights, even without aspirin She was breathless going upstairs, there was no chest pain but a slight dragging pain in the lower abdomen She kept about until the 8th day when she had a frontal headache and felt so wretched that she called the doctor

On examination the temperature was 100°F, pulse-rate 84 per minute, and respiration-rate 27 per minute She was pale and hollowed-eyed but not cyanosed The conjunctivæ were normal, there was enlargement of the lymphoid tissue on the posterior pharyngeal wall, but the throat was not red The right tonsillar lymphatic gland was palpable The chest showed a funnel deformity, and moved symmetrically The left lung base was dull to percussion posteriorly, breath sounds and vocal resonance were diminished over this area, and inspiratory crepitations were heard here and towards the midaxillary line

A normal temperature was recorded on the 13th day, the cough was persisting but the sputum was easier to raise and was occasionally mucopurulent The signs at the left base had disappeared except for râles, these persisted until the 16th day



Typical course of *Streptococcus* MG pneumonia.

when she was allowed up This patient received symptomatic treatment only

She was examined by the chest physician on the 16th day, posteroanterior and left lateral radiographs showed a patchy opacity *in the lingula* *Her* symptoms persisted for several more days, but 2 weeks later her chest radiograph was normal

Laboratory Findings

Throat washings (8th day) contained no bacterial pathogens Blood examination (8th day) hæmoglobin 12 4 g per 100 ml , red-cell count normal, white cells 7000 per c mm , differential count normal

Serum taken on 8th and 17th days agglutinated *Streptococcus* MG at dilutions of 80 and 320

Clinical, Radiological, and Laboratory Findings

Clinical Findings

Certain clinical features common to these 20 cases made bedside diagnosis possible The course of the disease is summarised broadly in the accompanying figure

The period of onset, from the first symptoms to the clinical recognition of pneumonia, was always a matter of days rather than hours, this is illustrated in table I

TABLE I—PERIOD OF ONSET

Onset (days)	No of cases
<5	7
5–10	8
>10	5

Of the 20 patients, 16 were so ill that they could not leave their beds for at least 10 days, the rest were able to get up within a week This constitutes one main difference between *Streptococcus* MG pneumonia and other common respiratory diseases seen in general practice

There was no significant sex difference, 12 cases being in females and 8 in males, the majority of the patients were between 20 and 55 years of age

The clinical features of the 20 cases are summarised in tables II and III

Symptoms or signs of upper-respiratory infection were not frequent, but when such inflammation was present it was slight None of the patients had a heavy cold or a very sore throat as an early symptom Some recalled having slight coryza or discomfort in the throat, in the majority the illness started as a " touch of 'flu " or " a chill " Examination of the upper-respiratory tract showed little abnormality, pus in the nose, œdema or reddening of the nasopharynx, or tender enlargement of cervical glands were never present

TABLE II—SYMPTOMS

Type	Symptom	No of cases
General	Headache	15
	Limb pains	13
	Lassitude	17
	Night sweats	14
	Rigors	10
Respiratory	Cough	20
	Coryza	8
	Sputum (early)	4
	Sputum (late)	12
	Sore throat	4
	Chest pain	11
	Dyspnœa	5
Alimentary	Anorexia	16
	Vomiting	3
	Abdominal pain	2

TABLE III—SIGNS

	Sign	No of cases
—	Fever	17
	Nasopharyngeal injection	3
Pulmonary	Bronchitis	2
	Pneumonia	19
	Collapse	2
Radiological	Pneumonia	20
	Collapse	3
	Effusion	1

The influenza-like symptoms lasted usually for a few days malaise, heaviness and aching of the limbs, and generalised headache were later overshadowed by prostration, cough, rigors, and night sweats 2 patients had pleuritic pain in the first few days of their illness, both had signs of segmental collapse 9 others had a dull, diffuse pain not related to respiration The cough was usually violent, spasmodic, and unlike the half-suppressed grunt heard in lobar pneumonia Because the cough was persistent, the patients lost sleep and became exhausted and hollow-eyed At first, there was little or no sputum, later it increased but remained mucoid during the 2nd and 3rd weeks of the illness As the sputum increased the cough became less troublesome In 4 cases recovery was interrupted by a relapse due to secondary bacterial infection the cough increased, there was much mucopurulent sputum, and there were signs of bronchitis (3 cases) or of bronchopneumonia (1 case) Slow progress towards recovery usually began in the 2nd week, and after the 3rd week there were no respiratory symptoms except slight cough Debility in convalescence was roughly proportional to the period of decubitus

The pulmonary physical signs suggested a slowly developing inflammatory process, often patchy, never reaching consolidation, and usually not resulting in obstruction of air passages to an extent detectable by auscultation Impairment of percussion note was seldom lobar in extent, and was commonly found at the lung bases The breath sounds were at first normal or slightly reduced, after 24 to 48 hours fine to medium râles were heard in these areas Voice conduction was normal or slightly reduced, but there were sometimes small patches of increased resonance and whispering pectoriloquy After 2 or 3 more days, fine crepitations were heard on deep inspiration, these disappeared gradually, over a variable period, leaving clinically normal lung

With so little respiratory embarrassment, signs of inadequate ventilation were few slight cyanosis was occasionally seen, but forced, shallow breathing was never observed

Radiological Findings

All the cases were examined clinically and radiologically by a chest physician The radiological picture was that of bronchopneumonia, but in 3 cases there was segmental collapse, 1 such case, in a child aged 8 years, showed hilar gland enlargement which subsided after 10 days Another case, presenting in the late stage of secondary bacterial infection, showed a dense basal shadow which was thought due to bronchial carcinoma, but the shadow diminished with penicillin therapy and eventually disappeared in 4 weeks In 1 case there was radiological evidence of pleural effusion

In 14 cases the sinuses were examined radiologically, there were no dense opacities or fluid levels to suggest inflammatory disease

Laboratory Findings

White-blood-cell counts were made in 8 cases only, usually as a diagnostic aid in the first day or two after pneumonia had been diagnosed In such cases the count was on the low side of normal, the differential count was

TABLE IV—DILUTIONS OF SERA AGGLUTINATING STREPTOCOCCUS MG

Case no	Days of illness			
	0–5	6–13	14–20	21 or more
1	<10	80		
2	<10	40		
3			40	20
4			320	320
5		80		
6		40		
7		40		
8		40		
9			160	
10	<10	20		
11				20
12			80	
13		80		80
14	20			80
15			80	
16	<10		40	
17		40	40	
18	<10	<10	20	40
19		80	320	
20	20	40	80	

normal, or there was a relative decrease in polymorphs In no case was the count higher than 12,000 cells per c mm

Serological findings—Serum was examined in all cases, in some single specimens were taken, in others two or more specimens were taken at intervals of about a week. Serological examination included tests for complement-fixing antibody to influenza virus A and B, the lymphogranuloma-venereum and ornithosis group of viruses, *Rickettsia burneti*, and latterly the adenoviruses None of the sera contained antibodies to these organisms at a significant level The antibodies to *Streptococcus* MG were estimated by a modification of the method of Thomas et al (1945), these results are summarised in table IV In cases with paired sera, a fourfold increase in titre was usual, in single sera a titre of 1/40 or higher was diagnostic The exception was case 11, which is included because of the clinical resemblance between his disease and that of his mother (case 10) Case 13, a chronic bronchitic, was found to have a titre of 1/80 on two occasions, 12 and 30 months after his illness, 3 years after his pneumonia he was subjected to pneumonectomy for removal of bronchial carcinoma The slow development of antibodies in case 18 suggests that absence of antibodies in the 2nd week does not preclude the diagnosis of *Streptococcus* MG pneumonia. In no case was the titre related to the clinical severity of the disease

Sputum examination—Naked-eye examination of the sputum at the bedside was often helpful in studying the course of the disease, it was commonly mucoid except when bacterial infection supervened, hæmoptysis was not observed 2 patients coughed up bronchial casts, which have formerly been associated with the diagnosis of plastic bronchitis Bacteriological examination of the sputum was made in 9 cases, the majority yielded no predominant organism, from 1 *Strep viridans* was isolated

Differential Diagnosis

Early clinical diagnosis of *Streptococcus* MG pneumonia is important because of the delay in reaching a serological diagnosis The differential diagnosis includes other common respiratory infections, which differ from virus pneumonia on the following points

Viral Infections

Influenza—This occurs sporadically, but more often in widespread and sometimes violent epidemics The clinical features are varied, but it has a sudden onset and there are signs of inflammation of the nasopharynx at some stage of the illness Influenzal pneumonia is nearly always of rapid onset, occurring within a few hours of the beginning of the primary illness It is usually associated with secondary bacterial infection, which is often staphylococcal (Stuart-Harris 1953)

Measles—This may be mistaken for *Streptococcus* MG pneumonia before the rash erupts Rashes are described in virus pneumonia, but these are usually urticarial or purpuric.

Adenovirus infections—The pulmonary physical and radiological signs of these infections are indistinguishable from those of other viral pneumonias, inflammation of the nasopharynx, cervical glands, or the conjunctivæ are diagnostic features

Bacterial Infections

Lobar pneumonia—" Classical " pneumonia is seldom seen in general practice nowadays It is commonly due to the pneumococcus It is rapid in onset, there are signs of lobar consolidation, and the pleuritic pain is responsible for suppression of cough and respiratory movement Such suppression and the loss of respiratory volume by consolidation lead to cyanosis and severe respiratory embarrassment, which are not often seen in *Streptococcus* MG pneumonia

Bacterial bronchopneumonia—Whatever the causal organism in this disease, the clinical features are fairly constant, though bacterial bronchopneumonia varies in degree and severity It is most often found in very young or old or debilitated patients Loss of resistance to invasion by organisms in the upper respiratory tract is the factor allowing the development of pneumonia, viral infections as a whole may induce this change. Influenza is the commonest precursor, but *Streptococcus* MG pneumonia may itself be responsible for bacterial bronchopneumonia

Pertussis—The spasmodic cough of this disease, when not accompanied by a whoop, sets a problem which can be solved only in the laboratory It is more easily recognised during epidemics, and only occasionally affects adults It is even more insidious than *Streptococcus* MG pneumonia, pulmonary physical signs in pertussis are often normal

Pulmonary tuberculosis—This used to be confused with viral pneumonia on radiological examination. The general practitioner is more likely to mistake *Streptococcus* MG pneumonia for pulmonary tuberculosis than the reverse. Malaise, lassitude, fever, night sweats, and cough are common to both diseases, amelioration with bed rest is more rapid in tuberculosis than in *Streptococcus* MG pneumonia

Discussion

Streptococcus MG pneumonia is a clinical entity, it runs a slow course and there are usually no signs of upper respiratory infection. According to Stuart-Harris (1953) *Streptococcus* MG antibodies are evoked only by the causal virus or group of viruses Cook et al (1960) implied that such antibodies were associated with the presence of Eaton agent

Cause

Liu et al (1957, 1959) have isolated a virus from cases of atypical pneumonia, they isolated fresh strains in the fertilised chick embryo and have shown a constant antigenic relationship between these strains and Eaton's virus There is no antigenic relationship between this virus and *Streptococcus* MG

Cook et al (1960), using the method described by Liu, have made independent isolations, but prefer the term Eaton agent to Eaton's virus Antibody to Eaton agent developed in 22 out of 26 cases of pneumonia with cold-agglutinins or *Streptococcus* MG antibodies Antibodies to Eaton agent were found in 26% of atypical pneumonias, without cold agglutinins or *Streptococcus* MG antibodies

Significance of Streptococcus MG Antibodies

If Eaton agent is the primary cause of *Streptococcus* MG pneumonia, it may also cause pneumonia without evoking the production of these antibodies *Streptococcus* MG is a non-pathogenic streptococcus, of the *Strep salivarius* group, commonly found in the mouths of healthy subjects It may act as a secondary invader in pneumonia caused by Eaton agent, but not by other respiratory viruses Thomas et al (1945) found *Streptococcus* MG in the lungs of 6 out of 8 patients who had died from atypical pneumonia, they were not able to isolate it from patients who had died from other causes This suggests that *Streptococcus* MG may have a pathogenic function in this type of pneumonia

Wormald et al (1956) showed that *Streptococcus* MG antibodies were present in significant amounts in the sera of subjects who had no recollection of recent respiratory illness Liu et al (1959) showed that antibody to Eaton agent decreased rapidly 3–4 months after the infective illness *Streptococcus* MG antibodies disappear at a comparable rate, though rarely they may persist at a high level at 12 months, case 13 in this series showed antibodies, at a dilution of 1/80, 2 years after the initial infection There is some evidence that *Streptococcus* MG antibodies, already present, may be increased by other intercurrent infections

Incidence

In my practice (urban, with some 3000 patients) 124 cases with lower respiratory illness were investigated serologically between January, 1952, and December, 1959 In 53 cases the serological findings were significant in 21 *Streptococcus* MG antibodies were found, serological diagnoses in the remainder were influenza (12), adenovirus infection (2), and inconclusive (18)

In 36 cases the initial clinical diagnosis was *Streptococcus* MG pneumonia, in 17 of these, the diagnosis was confirmed by finding *Streptococcus* MG antibodies The diagnosis was made with greater frequency and accuracy during the East Anglian outbreak of *Streptococcus* MG pneumonia described by Wormald et al (1956)

Treatment

Most cases recover with rest in bed, some without even this treatment, 2 of the cases in this series were ambulant throughout the illness, and a 3rd did not seek medical advice until he was laid low by secondary bacterial pneumonia Treatment of virus pneumonia with sulphonamides and penicillin has been recognised as valueless since their use became widespread These drugs may be actually harmful early in the disease, this is inferred by Auerbach et al (1952), and Parker et al 's (1947) crop of 8 postmortem cases had all had full courses of treatment with a sulphonamide

The contention that tetracyclines and similar wide-acting antibiotics have a specific action against this infection cannot be upheld On the other hand no published report has suggested that they are harmful, which means that they can be used with safety in general practice, as the patient with virus pneumonia may often be alarmingly ill, the use of tetracyclines may be a comfort to the physician

Conclusions

Streptococcus MG pneumonia is a complication of an infection which commonly manifests itself as a minor respiratory illness Incubation probably takes 2–3 weeks, and there is little evidence of nasopharyngeal inflammation by the time that signs of pneumonia are detectable The pneumonia runs a slow course, which may last 2 or more weeks, severe unproductive cough is the main symptom Painful pleural involvement, as in bacterial pneumonias, is rare Secondary bacterial infection may complicate convalescence, the resulting disease is clinically a bronchopneumonia with much mucopurulent sputum

The white-blood-cell count is usually normal in the early days of the disease, and in the absence of secondary bacterial infection counts above 10,000 per c mm are rare

The disease is associated with the production of antibodies to *Streptococcus* MG, these reach a maximum in the second week or later

More accurate laboratory methods of investigating *Streptococcus* MG pneumonia and allied diseases have been devised, but are too intricate for use in routine diagnostic laboratories Further additions to knowledge—concerning particularly the epidemiology, morbidity, and role of *Streptococcus* MG in this disease—may depend on more extensive use of laboratory tests Nevertheless, the diagnosis of *Streptococcus* MG pneumonia must be clinical, it can be made earlier by the general practitioner than by other clinicians

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FATTY-ACID DISTRIBUTION IN LIPIDS OF THE AORTIC WALL

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In a previous paper (Bottcher et al 1958) we presented some preliminary results of our analysis of lipids of the aortic wall at various stages of atherosclerosis At that time the analysis of the fatty-acid compositions of different lipid fractions could not be considered complete, for fatty acids having the same chain length but different degrees of unsaturation could not be satisfactorily separated by gas chromatography The advent of polyester stationary phases shortly afterwards made this possible A second series of analyses utilising these phases, and incorporating various other modifications and improvements into the analytical methods, led to the more detailed results which are presented here

Methods

Twenty-eight aortas, obtained from necropsy material, were used No material was accepted from patients who had been suffering from diseases known to be associated with gross disturbances of lipid metabolism Some, but not all, of the youngest (1–5 years) aortas had to be combined to provide sufficient lipid for analysis

The whole of the aorta, from directly behind the aortic valves to the iliac bifurcation, was used, the aortas were inspected and prepared in a fresh state. The external elastic membrane of the media, together with the adhering adventitia, was removed with the aid of a dissection microscope. The inclusion of most of the media with the intima in the material for analysis ensures, as formerly pointed out (Böttcher et al. 1958), strict comparability of the results for all stages of the disease.

The material was divided into four groups according to the macroscopic aspect of the aortic wall (Buck and Rossiter 1951, terminology modified in accordance with Classification of Atherosclerotic Lesions, W.H.O. 1958), as follows

Stage O no atherosclerotic lesions discernible at a magnification of 10

Stage I fatty streaks and/or spots present

Stage II fibrous plaques and/or atheroma present

Stage III lesions as above, with additional complications—e.g., ulceration, necrosis, hæmorrhage, thrombosis

The prepared material was cut into small pieces and freeze-dried. Extraction and analysis of the lipids into phospholipids, free fatty acids (F.F.A.), cholesterol esters (C.E.), and glycerides plus free sterols, and methylation of the fatty acids obtained from these four fractions, followed the methods described elsewhere (Böttcher et al. 1959b) Gas chromatography of the methyl esters was carried out on two columns prepared as there described, except for the use of a β-ray ionisation detector (W. G. Pye & Co.) instead of a gas-density balance and column temperatures of 204°C and 185°C for the non-polar (Apiezon L) and polar (maleic acid-adipic acid ethylene glycol polyester) phases respectively Fatty acids were identified and estimated by correlating for each methyl-ester mixture the chromatograms obtained from both stationary phases

The fatty acids found in C.E., F.F.A., and glyceride fractions of the lipids were on the whole well known and easily recognised, but those from the phospholipids contained a number of C_{22} and C_{24} acids which have not yet been completely isolated and identified. The formulæ of some of the phospholipid higher fatty acids in table II are therefore tentative, having been assigned on theoretical grounds from the gas-chromatographic observations In making these attributions, the consideration of "carbon-numbers" on two dissimilar stationary phases (Woodford and van Gent 1960) was useful. Work on these identifications is continuing

TABLE I—COMPOSITION OF LIPIDS FROM 23 AORTA PREPARATIONS AT DIFFERENT STAGES OF ATHEROSCLEROSIS

—	Stage of disease*				s†	P†
	O	I	II	III		
No of samples	6	6	6	5		
Average age (years)	47	20	56	51		
Average weight of lipids analysed (mg.) per preparation	44	108	638	1634		
Lipids as percentage of dry tissue (mean)	3·0	4·2	9·8	12·0	4·6	<0·0001
Mean composition of lipids:‡						
%Phospholipids	61·3	58·4	42·3	38·0	8·5	<0·0001
%Free fatty acids	8·5	4·2	1·4	1·0	3·5	<0·0001
%Free cholesterol	8·0	12·7	16·3	19·3	3·3	<0·0001
%Cholesterol esters	5·6	12·3	30·2	33·8	7·4	<0·0001
%Triglycerides	16·8	12·9	10·0	9·7	4·2	<0·0005

* For definition of stage of disease, see Methods.

† s = standard deviation calculated from the residual variance in the analysis of variance, it gives a pooled value of the standard deviations for all four stages P is the level of significance in the variance analysis.

‡ Phospholipids and free fatty acids were estimated gravimetrically cholesterol and triglycerides from colorimetric determinations of cholesterol and glycerol respectively For aorta lipids, the terms "cholesterol esters", "free cholesterol", and "triglycerides" are for practical purposes synonymous with "sterol esters", "free sterol" and "glycerides", since we have found that the sterol-ester fraction contains negligible quantities of sterols other than cholesterol the free-sterol fraction no more than 4% of other sterols mostly cholestanol (Woodford, unpublished results) and the glyceride fraction no more than 2% of mono- and diglycerides. Nevertheless, the terms are used strictly in this paper according to the context in which they appear

TABLE II—MEAN FATTY-ACID COMPOSITION OF LIPID FRACTIONS FROM UNDISEASED AND ATHEROSCLEROTIC AORTAS

Lipid fraction	Cholesterol esters		Glycerides		Free fatty acids		Phospholipids	
Stage of disease	O	II	O	II	O	II	O	II
No of samples	6	6	6	6	6	5	5	5
Fatty acids*								
10:0			0·1		0·1		0·1	
12:0	0·3	0·2	0·9	1·0	0·8	0·6	0·1	
14:0	1·9	1·4	3·5	3·4	2·5	1·8	0·6	0·8
14:1	0·1		0·1	0·1		0·1		
br-15:0	0·4	0·1	0·3	0·3	0·1	0·2		
15:0	0·6	0·2	0·9	0·4	0·5	0·4	0·2	0·2
15:1	0·2	0·1	0·3		0·3		0·1	
16:0	21·5	13·7	25·8	21·6	21·1	17·7	24·8	29·7
16:1	8·2	5·7	5·4	6·1	3·4	3·5	1·4	0·9
17:0	0·5	0·4	0·6	0·5	0·7	0·4	0·8	0·9
17:1	0·7	0·5	0·7	0·6	0·5	0·3	0·3	0·4
18:0	5·7	1·9	11·9	7·3	18·0	16·2	20·0	14·8
18:1	29·6	25·3	32·6	40·1	23·7	23·1	14·7	9·8
18:2	24·5	37·0	9·6	10·8	17·6	15·7	5·0	3·9
18:3	0·4	0·6	0·1	0·4	0·8	0·5		
20:0	0·2	0·4	0·4	0·2	0·3	0·3	1·5	1·8
20:1	0·9	0·2	1·1	0·7	0·6	0·7	0·8	0·6
20:2	0·1	0·3	0·3	0·5	0·4	0·2	1·1	0·5
20:3	1·2	2·2	0·6	0·6	0·7	1·6	2·1	1·7
20:4	2·1	5·1	2·7	2·9	5·5	12·1	9·9	9·4
20:5	0·2		0·3	0·2	0·2	0·4	2·1	1·1
22:0	0·1	0·3	0·6		0·5	0·2	1·6	4·5
22:1	0·2	0·5	0·2	0·5	0·1	0·3	1·0	1·5
22:2				0·1	0·1			
22:3			0·1	0·1	0·2	0·2		
22:4		0·1				0·6	0·1	
22:5	0·1	0·3	0·6	0·9	0·6	1·3	3·2	3·3
22:6	0·3	0·5	0·3	0·7	0·4	1·5	1·9	2·2
23:0							0·1	0·5
br-24:0							1·9	1·9
24:0					0·3	0·1	3·4	6·1
24:1							1·2	3·3
24:2								0·2

* For each acid, the initial figure gives the chain length. The symbol ":0" denotes saturated, ":1" monounsaturated, ":2" diunsaturated, etc., "br" denotes branched. See Dole et al. (1959)

Results

The mean lipid compositions of the four groups of aortas are presented in table I The relative amounts of different lipids change with the progress of the disease, with cholesterol and its esters rising and the percentage of the other lipid fractions falling The figures in table I are similar to those previously obtained (Böttcher et al 1959a, table 2) and statistical comparison of these overall lipid compositions with all those obtained to date (50 in number) showed in fact that the twenty-three aorta preparations analysed were, judged by this criterion, typical examples of the stage of disease to which they had been allotted

If the lipid fractions are expressed as weight percentages of the dry tissue, the amounts of most of the fractions, including phospholipids and triglycerides, can be seen to increase from stage O to stage III The only exception is the F.F.A., which on the contrary decrease. This could be an indication of the lower metabolic activity of the diseased wall.

The most striking aspect of the fatty-acid analyses, which are shown in succeeding tables, was the relative constancy of the fatty-acid patterns for each lipid fraction Individual variations are considerable, and are superimposed on changes in the mean values which can be significantly correlated with the disease, but none of these changes are great enough to distort the characteristic fatty-acid distribution These distributions are so typical that it is possible to discern by mere inspection of the gas chromatogram from which lipid fraction the fatty-acid mixture under investigation has been derived.

We shall not here present the complete fatty-acid analyses of the 16 groups of lipids (phospholipid, F.F.A.,

TABLE III—CHOLESTEROL ESTERS OF AORTA: MEAN PERCENTAGES OF INDIVIDUAL ACIDS AND COMBINATIONS OF ACIDS FOR FOUR STAGES OF ATHEROSCLEROSIS

—	Stage of disease				s	P
	O	I	II	III		
No. of samples	6	6	6	5		
% Palmitic (16:0)	21·5	16·0	13·7	13·2	4·2	0·01
% Palmitoleic (16:1)	8·2	6·0	5·7	5·0	1·7	0·02
% Stearic (18:0)	5·7	3·6	1·9	1·6	1·4	0·0004
% Oleic (18:1)	29·6	32·3	28·3	30·2	4·6	0·5
% Linoleic (18:2)	24·5	30·0	37·0	36·0	4·8	0·0008
% Eicosatrienoic (20:3)	1·2	2·5	2·2	3·0	1·6	0·4
% Arachidonic (20:4)	2·2	2·6	5·1	4·7	1·7	0·01
% Saturated	31·2	22·9	18·7	17·0	5·4	0·002
% Monounsaturated	39·9	39·9	35·1	36·7	5·0	0·3
% Polyunsaturated	28·9	37·2	46·2	46·3	5·6	<0·0001

C.E., and glyceride, in stages O, I, II and III), but mean values for undiseased and diseased stages (namely, stages O and II) are shown in table II. Standard deviations are not shown, since these are quoted for the most prominent acids in later tables.

Tables III–VI show the variation of the quantitatively most important acids with stage of disease, for each of the lipid fractions. The second half of each table gives the sums of saturated, monounsaturated, and polyunsaturated acid percentages.

These summations have been made to facilitate examination of the suggestion of various authors (e.g., Sinclair 1956, Luddy et al. 1958) that cholesterol esters of saturated and/or monounsaturated acids tend to be deposited in the arterial wall with the formation of atheroma. If this were true, one would presumably expect to find an ever-increasing proportion of these acids in the artery wall with increasing severity of the lesions. One observes, on the contrary (table III), a marked increase in the polyunsaturated acids, coupled with a decrease in all saturated acids. Both these changes are statistically highly significant.

TABLE IV—GLYCERIDES OF AORTA: MEAN PERCENTAGES OF INDIVIDUAL ACIDS AND COMBINATIONS OF ACIDS FOR FOUR STAGES OF ATHEROSCLEROSIS

—	Stage of disease				s	P
	O	I	II	III		
No. of samples	6	6	6	5		
% Myristic (14:0)	3·5	3·6	3·4	2·8	0·8	0·5
% Palmitic (16:0)	25·8	25·0	21·6	23·0	3·4	0·2
% Palmitoleic (16:1)	5·4	5·3	6·1	5·2	0·9	0·3
% Stearic (18:0)	11·9	10·8	7·3	7·3	2·1	0·002
% Oleic (18:1)	32·6	33·8	40·1	35·4	4·9	0·08
% Linoleic (18:2)	9·6	10·5	10·8	12·6	3·4	0·5
% Eicosatrienoic (20:3)	0·6	0·7	0·6	1·6	0·6	0·04
% Arachidonic (20:4)	2·7	2·6	2·9	3·9	1·0	0·2
% Saturated	44·9	42·8	34·7	35·3	5·7	0·01
% Monounsaturated	40·4	41·8	48·0	43·3	4·7	0·06
% Polyunsaturated	14·7	15·4	17·3	21·4	5·2	0·2

According to Sinclair (1959), cholesterol esters of "abnormal" polyunsaturated acids—i.e., with double bonds in different positions from those in the essential fatty acids (E.F.A.) or with the *trans*- instead of the *cis*-configuration, are also likely to be found in atheroma. Such acids could have the same gas-chromatographic characteristics as the true E.F.A., and therefore be mistaken for them. For this reason the major polyunsaturated acid of the cholesterol esters, 18:2, was examined further to see whether it was identical with linoleic acid or not.

Several stage-II aorta preparations were pooled, and the cholesterol-ester fatty acids (C.E.F.A.) isolated. Preparative gas chromatography on Apiezon yielded 20 mg. of the methyl ester of 18:2 contaminated with some 18:1. Ozonolysis, oxidation, *and methylation yielded azelaic* (C_9 dibasic) and caproic (C_6) acids, with less than 9% of other acids (discounting pelargonic acid, *from the* oleic acid). Infra-red spectroscopic analysis (kindly carried out by Unilever Research Laboratory, Vlaardingen) gave a maximum of 2% *trans*-double bonds.

The conclusion is inescapable that the acid measured as 18:2, which comprises almost all of the dienoic acids and forms the major component of the polyunsaturated acids, is in fact at least 90% true linoleic acid (cis, cis-9, 12-octadecadienoic acid).

The structure of the other polyunsaturated acids detected (which include, approximately in descending order of magnitude, 20:4, 20:3, 20:5, 20:2, 22:5 and 22:6) has not yet been so firmly established. However, it can be seen from the tables that the percentage of each of these individual acids changes with the stage of the disease in the same sense as that of linoleic, so that the polyunsaturated acids can, at any rate in the present study, be regarded as a homogeneous group.

TABLE V—FREE FATTY ACIDS OF AORTA: MEAN PERCENTAGES OF INDIVIDUAL ACIDS AND COMBINATIONS OF ACIDS FOR FOUR STAGES OF ATHEROSCLEROSIS

—	Stage of disease				s	P
	O	I	II	III		
No. of samples	6	6	5	5		
% Palmitic (16:0)	21·1	19·1	17·7	18·0	4·0	0·5
% Palmitoleic (16:1)	3·4	3·3	3·5	4·3	1·5	0·6
% Stearic (18:0)	18·0	16·8	16·2	14·2	4·3	0·5
% Oleic (18:1)	23·7	22·3	23·1	23·3	4·1	0·9
% Linoleic (18:2)	17·6	18·7	15·7	19·2	6·2	0·8
% Eicosatrienoic (20:3)	0·7	1·1	1·6	1·9	0·9	0·2
% Arachidonic (20:4)	5·5	8·0	12·1	9·5	4·9	0·2
% Saturated	44·9	41·5	37·9	36·9	8·2	0·4
% Monounsaturated	28·6	27·1	28·0	29·3	4·6	0·9
% Polyunsaturated	26·5	31·4	34·1	33·8	8·9	0·5

It is worth noting that almost the whole of the trienoic acid in aorta consists of 20:3, and that linolenic acid, assumed by other workers to be the main trienoic acid constituent, contributes to the total in only trace amounts.

The analysis of variance of the figures in tables I and III–VI showed that differences between stages O and I or between stages II and III were of low or negligible significance; where a high level of significance is shown, it refers to the difference between O or I on the one hand and II or III on the other.

The changes in *glyceride* fatty acids (table IV) are similar to those in cholesterol esters, with a fall in saturated acids balancing a rise in polyunsaturated acids. These changes are, however, much less significant than in the cholesterol esters. An "out-

TABLE VI—PHOSPHOLIPIDS OF AORTA: MEAN PERCENTAGES OF INDIVIDUAL ACIDS AND COMBINATIONS OF ACIDS FOR FOUR STAGES OF ATHEROSCLEROSIS

—	Stage of disease				s	P
	O	I	II	III		
No. of samples	5	4	5	5		
% Palmitic (16:0)	24·8	28·1	29·7	29·9	2·6	0·03
% Palmitoleic (16:1)	1·4	0·8	0·9	1·1	0·4	0·2
% Stearic (18:0)	20·0	18·6	14·8	15·1	2·3	0·005
% Oleic (18:1)	14·7	11·4	9·8	9·7	2·7	0·04
% Linoleic (18:2)	5·0	4·4	3·9	4·2	2·0	0·8
% Eicosatrienoic (20:3)	2·1	1·6	1·7	1·8	0·6	0·5
% Arachidonic (20:4)	9·9	10·1	9·4	7·4	2·5	0·3
% Behenic (22:0)	1·6	3·4	4·5	4·4	1·1	0·003
% Lignoceric (24:0)	3·4	3·8	6·1	6·4	2·3	0·15
% Tetracosenoic (24:1)	1·2	1·5	3·3	4·7	2·0	0·06
% Saturated	55·2	59·4	61·2	62·0	5·0	0·2
% Monounsaturated	19·4	15·6	16·6	16·6	3·3	0·3
% Polyunsaturated	25·4	25·0	22·2	21·4	3·7	0·3

of-line" result is the sudden rise in monounsaturated acids between stages I and II, whereas the value for stage III is not significantly different from that in stage I. The relative prominence of myristic acid, always between 3 and 4%, for glyceride fatty acids is interesting: for other lipid fractions this percentage is 1 to 2, in phospholipids less than 1.

Table V shows trends in mean values in the *free fatty acids* which are similar to those in C.E. and glyceride, but which are in no case statistically significant.

Although these three fractions show similar changes, one figure is especially characteristic of the C.E.F.A.—namely, the ratio of linoleic to stearic acid. For glyceride and F.F.A., this ratio is low and increases very slightly from stage O to stage III (1·0 to 1·9), whereas for C.E. it is high, and increases several-fold (stage O, 4·7, I, 19·2, II, 21·1, III, 24·2). The ratio changes so dramatically that it can almost be regarded as an index of the degree of atherosclerosis in the aortic wall (Böttcher 1960).

The *phospholipids* present a quite different picture (table VI). Phospholipid fatty acids are characterised by a high degree of saturation, and this actually increases (though slightly) with the severity of the lesions. This is the resultant of a decreasing stearic-acid content coupled with increases of palmitic acid and of two new acids of consequence—C_{22} and C_{24} saturated. The initial fall and subsequent rise of the monounsaturated total is largely due to the opposing trends of oleic acid and a third typical "phospholipid" acid, C_{24} monoenoic. The polyenoic acids show a decrease from stage O to stage III, a decrease in which linoelic acid plays only a small and irregular part.

These irregular variations in individual acids, and the contrary behaviour of different acids of the same degree of unsaturation (e.g., palmitic and stearic, oleic and 22:1), are in contrast with the smooth and consistent changes with disease shown in the other lipids. The phospholipids differ from the other lipid fractions in being a mixture, consisting of at least four major classes of compound (cephalins, lecithins, sphingomyelins, lysolecithins). The irregularly changing fatty-acid compositions mainly reflect changes in the ratios of these four classes, each having its characteristic fatty-acid pattern, rather than variations in the fatty-acid make-up of any phospholipid class. We have established that, in common with sphingomyelins from other sources, artery sphingomyelins contain an unusually high proportion of C_{24} acids, a small percentage of oleic acid, and virtually no polyunsaturated acids. We have also found, in agreement with Buck and Rossiter (1951) and Smith (1959), that the ratio of sphingomyelins to other phospholipids increases with the stage of the disease. These facts account for most of the changes found in the total phospholipid fatty acids. Details of the phospholipid analyses will be published later.

Discussion

Aorta Cholesterol Esters

In examining fatty-acid compositions, most other workers have confined themselves to those of the cholesterol esters, and their figures may be compared with the relevant portion of our results. Recently, Wright, Pitt, and Morton (1959) published figures which they pointed out to be in disagreement with those of other authors working on cholesterol esters from atheromatous aortic tissue, though in moderate agreement with our previous, incomplete results.

It is evident from table VII that our newer results are in fair, but only fair, agreement with those of Wright et al., the important differences being that we find higher dienoic and lower saturated-acid percentages for stages II and III than they do in plaques. The agreement is closer than previously, in particular in that our newer methods have led to the observation of a lower figure for monoenoic acids. The remaining differences could be due to either or both of two factors: (1) differences in extraction technique, in that grinding of the tissue under ether according to Wright et al. might conceivably lead to oxidation and loss of dienoic acid, or (2) differences in the estimation method. At first sight gas chromatography seems preferable to the alkali isomerisation used by Wright et al. in that the individual acids can be recognised and separately estimated, though as a technique it is also not without its difficulties. It is perhaps significant that our results are most nearly in accord with those of Tuna et al. (1958), who employed gas chromatography for the determination of the percentages of saturated and monounsaturated acids.

TABLE VII—CHOLESTEROL-ESTER FATTY ACIDS IN ATHEROMATOUS AORTAS

—	Present authors				Wright et al (1959) Plaques and walls	Tuna et al (1958) Plaques	Luddy et al (1958) Plaques
	Stage O	Stage I	Stage II	Stage III			
% Saturated	31·2	22·9	18·7	16·1	26·1	10·7	4·2
% Monoenoic	39·9	39·9	35·1	37·5	35·1	41·3	61·5
% Dienoic	24·6	30·8	37·3	37·2	29·5	37·6	23·6
% Trienoic	1·6	2·8	2·8	3·4	3·0	1·6	1·4
% Tetraenoic	2·1	2·7	5·3	4·6	4·7	7·4	7·0
% Pentaenoic	0·3	0·6	0·3	0·8	1·0	0·9	1·3
% Hexaenoic	0·3	0·3	0·5	0·4	0·5	1·0	1·0

In any case, it is clear that the results of Luddy et al. (1958) differ widely from all others given. Their value of 61·5% for monoenoic acids, which was obtained by difference, is 15% higher than the highest value we have ever found by direct measurement and addition. Similarly, the lowest percentage of saturated acids we have observed in any individual case is 11·2, compared with their 4·2.

The main interest of our results lies in the examination of aortas in three stages of atherosclerosis, compared with apparently undiseased aorta. The C.E. show, in opposition to what is predicted by the E.F.A. hypothesis, increases in linoleic and all polyunsaturated acids. Saturated cholesterol esters, far from being preferentially deposited, decrease sharply in percentage from undiseased to diseased aortas. These changes in fatty-acid composition are the most striking to be seen in any of the lipid fractions, and are statistically highly significant.

Comparison with Plasma Cholesterol Esters

One of the main theories of atherogenesis postulates that the lipids found in arterial deposits originate in the blood. Some light can be thrown on whether this is so, and if so whether the deposition is indiscriminate or selective, by comparing the fatty-acid compositions of the deposited lipids with those found in plasma. The determinations of unsaturated acids in plasma-cholesterol esters by different authors are, in contrast with those in atheromas, in moderate agreement with one another (table VIII).

The mean values for dienoic acids lie between 35 and 50%. Our figures (table VII) for C.E. dienoic acids in stages II and III coincide with the lower end of this range (cf. those for the plasma of atherosclerotic patients), and the values for the other polyunsaturated and for the satu-

TABLE VIII—CHOLESTEROL-ESTER FATTY ACIDS IN PLASMA FROM NORMAL AND ATHEROSCLEROTIC SUBJECTS

—	Wright et al. (1959) Normal	Luddy et al. (1958) Normal	Tuna et al (1958) Normal	Schrade et al (1959)		
				Normal	Atherosclerotic	Diabetic
% Saturated	11·9 ± 3·9	18·7	16·2			
% Monoenoic	32·7 ± 6·9	23·5	28·6			
% Dienoic	43·8 ± 3·5	47·5	41·1	47·1 ± 1·2	38·0 ± 1·1	37·7 ± 1·2
% Trienoic	4·0 ± 0·8	0·7	0·7	0·8 ± 0·06	1·5 ± 0·09	1·6 ± 0·11
% Tetraenoic	6·1 ± 1·5	8·0	6·2	6·3 ± 0·2	5·0 ± 0·2	4·4 ± 0·2
% Pentaenoic	0·8 ± 0·3	0·9	0·7			
% Hexaenoic	0·7 ± 0·4	0·7	1·2			

rated CEFA are also not significantly different from those in plasma A weak case could be made out for a preferential deposition of monoenoic acids, but there is nowhere an indication of marked specificity in the kind of acid deposited On the contrary, the impression is that the aortic CE are deposited from plasma in an indiscriminate non-specific way which results in the CEFA in the arterial wall having the same composition as in plasma Furthermore, the animal organism is generally supposed not to be able to synthesise linoleic acid (though see James et al 1959), so the fact that the percentage of CE linoleic acid is as high in the deposits as in plasma implies that the whole of the CE derive from the blood and are not to any appreciable extent diluted with CE synthesised in the aortic wall

Comparison of Glycerides, Free Fatty Acids, and Phospholipids of Aorta and Plasma

A similar comparison of fatty-acid compositions of glyceride, FFA, and phospholipid fractions of blood and aorta lipids is instructive The analyses of plasma lipids by Schrade et al (1959) are based on methods similar to our own, except for the final estimation, which used an alkali isomerisation method Unfortunately, saturated and monoenoic acids were not determined by these authors, so that complete comparison is impossible However, enough data are available to show (table IX) that the values for glyceride acids in aorta and plasma resemble one another, but that the dienoic-acid contents of FFA and phospholipid are extremely dissimilar

TABLE IX—FATTY ACID COMPONENTS OF GLYCERIDES, FREE FATTY ACIDS AND PHOSPHOLIPIDS IN AORTA AND PLASMA

—	Present authors intima and media				Schrade et al (1959) plasma		
	Stage O	Stage I	Stage II	Stage III	Normal	Athero-sclerotic	Diabetic
Glycerides							
% Dienoic	10 0	10 8	11 4	13 4	11 2	10 9	10 8
% Trienoic	0 8	1 0	1 1	1 8	0 9	0 7	0 7
% Tetraenoic	2 7	2 8	2 9	3 9	1 5	0 8	0 7
Free fatty acids % Dienoic	18 1	18 8	15 9	19 7	4 0	2 9	3 1
Phospholipids							
% Dienoic	6 1	6 0	4 5	6 4	22 2	19 6	19 8
% Trienoic	2 1	1 8	1 7	1 8	0 7	1 2	1 3
% Tetraenoic	10 0	11 0	9 4	8 1	6 6	4 5	4 6

A closer comparison is possible with the results of Dole et al (1959) on plasma lipids, since these authors determined fatty-acid composition by gas chromatography As they did not separate the CE from the glyceride fraction, only the FFA and phospholipid fractions can be compared (table X) For the FFA there is in this case no great difference between aorta and plasma lipids the patterns are similar, with the reservation that in the aortic wall the percentage of oleic acid is lower, that of polyunsaturated acids somewhat higher The discrepancy between the results of Dole et al and those of Schrade et al could be due to the use by the latter of ion-exchange resins for extraction of the FFA in our experience, the use of these resins leads to degradation

The difference between aorta and plasma phospholipid is, however, confirmed the lower percentages of oleic and linoleic acids found in the deposits are striking The figure of 14% for phospholipid linoleic acid has also been obtained in this laboratory in the two preliminary analyses of plasma lipids so far completed, so the difference between aorta and plasma phospholipid is not a question of differing laboratory techniques Two possible explanations of this phenomenon are that one of the phosphatides of blood preferentially accumulates in atheromas, as discussed above, or that the phospholipid of aorta are synthesised in situ and do not originate in plasma at all The work of Zilversmit and McCandless (1959) shows that the aortic wall is an active site for phospholipid synthesis, at least in the rabbit

TABLE X—COMPARISON OF INDIVIDUAL ACID PERCENTAGES IN FREE FATTY ACIDS AND PHOSPHOLIPIDS OF AORTA AND PLASMA

—	Free fatty acids			Phospholipids		
	Intima and media		Plasma (Dole et al 1959)	Intima and media		Plasma (Dole et al 1959)
	Stage O	Stage III		Stage O	Stage III	
% Palmitic	21 1	18 0	23 2	24 8	29 9	33 1
% Palmitoleic	3 4	4 3	2 4	1 4	1 1	2 5
% Stearic	18 0	14 2	12 9	20 0	15 1	12 8
% Oleic	23 7	23 3	32 6	14 7	9 7	18 6
% Linoleic	17 6	19 2	14 3	5 0	4 2	16 0
% Eicosatrienoic	0 7	1 9	1 3	2 1	1 8	1 8
% Arachidonic	5 4	9 5	4 7	9 9	7 4	4 3

Still more detailed analyses of aorta and blood lipids are needed to distinguish between these possibilities, and these are already in progress

Lipids of Other Arteries

The overall composition of lipids from coronary arteries differs considerably from that of aorta lipids (Bottcher et al 1959a) We have been investigating whether the changes in the fatty-acid compositions of lipid fractions with aortic atherosclerosis are to be found in comparing undiseased and atherosclerotic coronary arteries and with similar arteries from the circle of Willis This programme has suffered some delay because of the difficulty of obtaining sufficient quantities of lipid from the undiseased tissues, but the results will be reported in due course There do seem to be some differences in the observed fatty-acid compositions—for example a higher oleic-acid percentage in the triglycerides of atherosclerotic coronary arteries than in the corresponding fraction from aorta

Summary

The analysis of lipids from preparations of intima and media from young undiseased aortas and from aortas in three stages of atherosclerosis is described The lipids were separated into phospholipids, free fatty acids (FFA), cholesterol esters (CE), and glycerides plus free sterols, and the fatty acids obtained from these four fractions were analysed by gas chromatography

The most striking changes were observed in the cholesterol-ester fatty acids (CEFA), in which with increasing atherosclerosis of the artery the polyunsaturated acid percentage rises from 29 to 46% and the saturated acids decrease from 31 to 17%, while the monounsaturated acids show no significant change It was established that the main component of the CE polyunsaturated acids, octadecadienoic acid, is linoleic acid and not an isomer of it

Similar, but smaller changes were found in the FFA and glyceride fatty acids Phospholipid changes are different and more variable, and probably reflect changes in the ratio of the different phosphatides to one another

The bearing of these results on current theories of atherogenesis is discussed

Preliminary findings on the lipids of coronary arteries and brain arteries are mentioned

These investigations have been made with the support of the Netherlands Organisation for the Advancement of Pure Research

(Z W O) and the Netherlands Organisation for Health Research (T N O) We are indebted to the Laboratory of Pathological Anatomy at Leiden for access to the necropsy material and facilities for its dissection, and to Dr J Zeldenrust of the State Laboratory for Forensic Medicine, The Hague, for supplying much further material We gratefully acknowledge the collaboration of Dr E F Drion of the statistics department of T N O, in the statistical treatment of the results, and the skilled analytical assistance of Miss H A M ter Haar, Miss M Kooiman, and Mr G F G Clemens

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PULMONARY ALVEOLAR PROTEINOSIS

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IN 1958 Rosen, Castleman, and Liebow summarised 27 cases of an apparently new entity to which they gave the name of "pulmonary alveolar proteinosis" This name was based on the histological appearances, which are characterised by a peculiar alveolar consolidation of protein-like material with a surprising absence of inflammatory infiltration The majority of their cases were adults aged 20 to 50, with a male preponderance of 2 5 1 The predominating symptom is progressive dyspnœa, usually insidious in onset, although sometimes preceded by one or more febrile illnesses often thought to be pneumonic Once the illness is established, fever is not a feature Other common symptoms are cough (usually productive but occasionally blood-stained), fatigue, chest pain, and slight loss of weight Rosen et al describe the X-ray appearances as fine, diffuse, perihilar radiating shadows, feathery or vaguely nodular, resembling in their "butterfly" distribution the pattern seen in severe pulmonary œdema The clue to the diagnosis, they say, is that the symptoms are inappropriate to the gross radiological changes The diagnosis can be firmly established only by lung-biopsy

The 27 cases of Rosen et al had been collected over five years, 24 coming from scattered parts of the United States and 1 each from England, Canada, and Italy Since then four reports from America (Friedman and Strickland 1958, Lull et al 1959, Landis et al 1959, Moertel et al 1959) together add another 5 cases, and a 6th has been recorded in New Zealand (McDowell et al 1959) All these reports substantiate the main features of the original large series The case here reported also follows the same general pattern Rosen and his colleagues noted that cases seemed to be coming to their notice with increasing frequency, and more general recognition of the disease may perhaps reveal that it is also not a rarity in Great Britain

Case-report

A man, aged 35 in 1958, had been a coal-miner since he was 14, and had also worked part-time on a farm since the summer of 1957 From the beginning of 1958 he had occasional chest pains and was sometimes short of breath at work, but he did not seek medical advice In June, 1958, when mass radiography was carried out at the pit, his chest was regarded as clear, and this was reaffirmed when the film was checked in the light of later developments In July he was treated with antibiotics at home for what appeared to be right-sided pneumonia During this episode, although never afterwards, he had slightly bloodstained sputum He returned to work, but he did not feel well, becoming increasingly breathless on exertion, and had to stop work again after two weeks He had a troublesome cough, mainly dry but productive of grey sputum in the mornings Night-sweats occurred and he lost 14 lb in weight in two months

Progress of Illness

When he was admitted to the Nottingham City Hospital on Sept 14, 1958, his temperature was 99 8°F, but it fell the same day and never rose above 99°F during his three weeks' stay The only physical sign was slightly diminished air entry, with impaired percussion note, at the left base Radiography showed shadows in the left mid-zone and right base, consisting of multiple minute opacities (fig 1) The white-cell count was 8700 per c mm with 78% neutrophils Friedländer's bacillus was cultured from the sputum but no tubercle bacilli were found or grown either then or subsequently He was treated with penicillin at first, and then with streptomycin There was slight clearing of the X-ray film but some diffuse shadowing persisted. He was discharged on Oct 8 with a diagnosis of atypical pneumonia

During the next six months he was admitted to hospital three times The first two readmissions were prompted by recurrence of cough and pain in the chest, although throughout

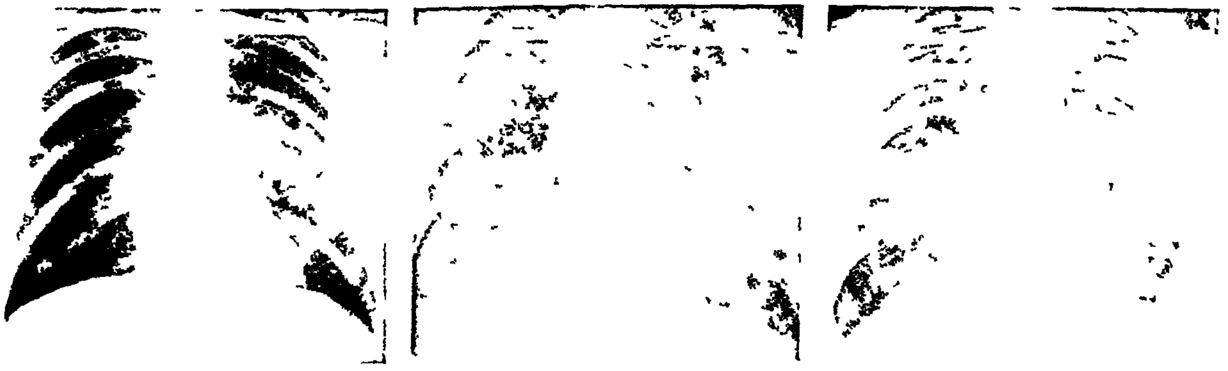

Fig 1 Fig 2 Fig 3

Figs 1 to 3—X-ray appearances (1) on admission to hospital in September, 1958; (2) at the time of lung biopsy in April, 1959 (3) in July, 1959, after return home

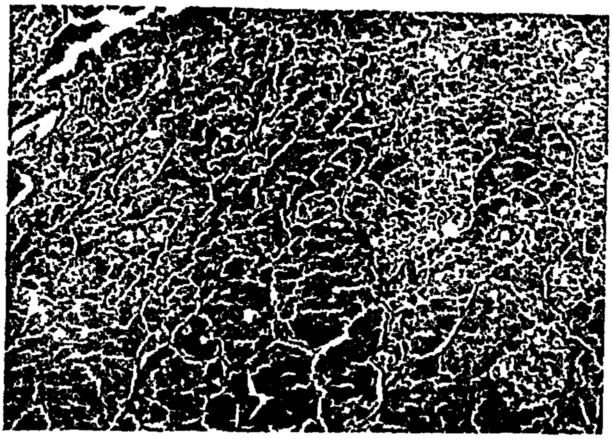

Fig 4—Lung biopsy Diffuse consolidation with finely granular "proteinaceous" material (Hæmatoxylin and eosin ×33)

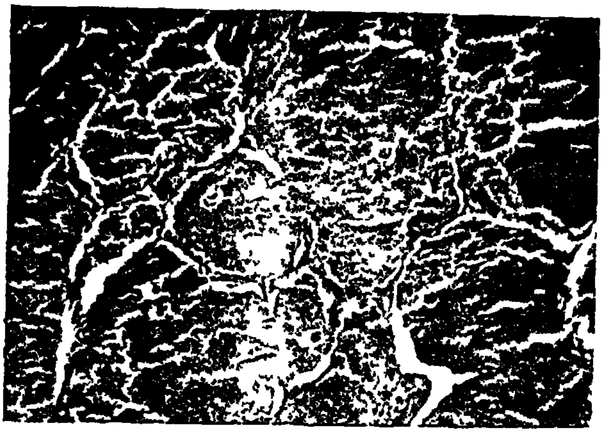

Fig 5—Lung biopsy Higher-power view of several alveoli to show absence of inflammatory infiltration Only a very occasional large mononuclear cell is seen (H & E ×100)

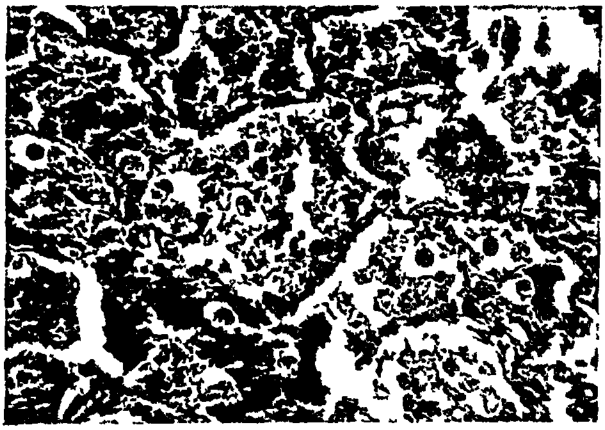

Fig 6—Lung biopsy A group of alveoli containing numerous large mononuclear cells ("septal cells") The "proteinaceous" material, staining darkly with P A S, is more sparse here It is seen most prominently towards the lower left-hand corner where the mononuclear cells are fewer. (P A S ×225)

the illness increasing dyspnœa on exertion was the predominant symptom Radiological examinations, in spite of minor fluctuations, showed gradually extending opacities, almost fluffy in type, involving both the lungs, but especially the left, and maximal in the perihilar regions (figs 1–3)

When he was admitted for the third time, in January, 1959, further investigations were undertaken with a view to excluding polyarteritis nodosa and sarcoidosis There was little support for the former diagnosis, pyrexia being insignificant, eosinophilia absent, and muscle biopsy negative From the X-ray appearances, sarcoidosis seemed a more likely possibility although enlargement of the hilar lymph-nodes was not detected However, biopsy of the scalene lymph-node was negative, and, whereas the Mantoux tuberculin test was negative at a dilution of 1/1000, it was positive at 1/100 It was at this stage that lung biopsy was proposed to establish a diagnosis, but the patient's response to premedication was such that it seemed likely that a general anæsthetic might be dangerous This was thought to be due to recent treatment with prednisone, which had been discontinued because it appeared ineffective

Lung biopsy was therefore postponed for two months, and he was readmitted on April 7, 1959 At this time, he was symptomless apart from exertional dyspnœa, chest signs were negligible but X-ray changes were extensive (fig 2) A left thoracotomy was performed on April 28 The lung felt generally granular, with firmer areas in the lingula and posterior upper zone The tip of the lingula was amputated The fluid which exuded from the cut surface resembled pus, but microscopically pus cells were absent, no organisms were detected, and cultures were sterile

Histology of Lung

There were extensive areas of confluent consolidation of unusual type The alveoli were distended with finely granular eosinophilic material (fig 4) Inflammatory infiltration was absent (fig 5), but there were infrequent large foamy mononuclear cells (the "septal cells" of Rosen et al), mostly collected within scattered small groups of alveoli (fig 6) The eosinophilic material gave a strongly positive periodic-acid/Schiff (P A S) reaction, and frozen sections stained with Sudan and oil red dyes showed fairly diffuse fine deposition of lipoid, with increased amounts in the mononuclear cells, whose cytoplasm stained with P A S Stains appropriate for bacteria, fungi, and pneumocystis were negative These included Gomori's methenanamine/silver-nitrate method (Grocott 1955), which has been found especially suitable for pneumocystis All these histological findings were typical of pulmonary alveolar proteinosis

Further Course

The patient has not been able to return to work and his activities are considerably restricted by breathlessness Last July the X-ray changes had increased (fig 3) and the films taken in October show no improvement

Discussion

The present case illustrates most of the features of pulmonary alveolar proteinosis and gives some indication of the commoner diagnoses which are likely to be considered Of these, sarcoidosis causes the most confusion and has figured as a provisional diagnosis in many of the reported cases The radiological appearances have some similarities, the main features distinguishing pulmonary alveolar proteinosis from sarcoid being the predominance of perihilar shadows, the irregular distribution elsewhere, and (most characteristic of all) the absence of hilar lymph-node enlargement

Two other diagnoses require brief mention in this case The patient having been a coalminer for twenty years, pneumoconiosis was obviously thought of, but the X-ray changes were not consistent with this Another occupation which could have had some bearing was part-time employment on a farm, and "farmer's lung" therefore required exclusion, especially as the patient thought that dyspnœa was more noticeable while working on the farm than in the mine "Farmer's lung" seems to be related to the inhalation of dusts from mouldy hay or corn crops (Dickie and Rankin 1958) There had, in fact, been no exposure to mouldy crops, and, without going into details here of the clinical and radiological differences, "farmer's lung" has a totally different histology, consisting of a granulomatous (sometimes tuberculoid) interstitial infiltration.

The histology of pulmonary alveolar proteinosis bears resemblance to only one other condition—namely, pneumocystis infection However, pneumocystis pneumonia, generally regarded as synonymous with interstitial plasma-cell pneumonia (Gajdusek 1957), is a disease of young infants the organism *Pneumocystis carinii*, which is held responsible for it has been found only in a few instances in adults (Hamperl 1956) and these appear to have been secondary infections Rosen et al noted certain similarities between the pathological appearances of pneumocystis pneumonia and pulmonary alveolar proteinosis, but they described distinguishing features and they could not find the pneumocystis parasite in their cases Moreover, Hamperl saw the sections of 2 of their cases in 1955 and agreed that it appeared to be a different entity

Other possible ætiological factors can be put forward only very tentatively Rosen et al discuss in general terms the possibility that some relatively recently introduced inhalant, perhaps of a chemical nature, might be responsible They note also that 4 of their patients worked in or about lumberyards and one was a carpenter The patient of Moertel et al 's report had formerly been a lumberyard worker and carpentry was his hobby Rosen et al do not indicate how this rather broad occupation group could be linked with pulmonary alveolar proteinosis, and whether or not inhalation of wood dust could be held responsible Our patient's work did not especially bring him in contact with wood or wood dust Apart from this group, the recorded occupations have been widely scattered and no other miner appears among the cases reviewed

The prognosis of pulmonary alveolar proteinosis is difficult to assess as yet Rosen et al said that 8 of their patients had died, while in 13 the symptoms had persisted, with varying intensity, for periods between five and thirty-five months Only 1 patient had apparently fully recovered, although 4 more were definitely improved at the time of their publication Another of Rosen's cases has since proved fatal (personal communication from Plenk, cited by Lull et al 1959) The patient of McDowell et al 's report had much improved and was almost clear radiologically fifteen months after lung biopsy Authors of other recent reports have not followed up their cases sufficiently long to provide any useful prognostic data, but I know of no other fatal cases

Rosen et al did not feel that treatment with adrenocorticoids or various antibiotics affected the course of the disease, although antibiotics appeared to be useful in terminating febrile episodes This seemed to be equally true in the present case Moertel et al thought that prednisone was responsible for clinical improvement in their single case but it did not prevent X-ray recurrence three months later The patient of McDowell et al who showed sustained improvement both clinically and radiologically, had been treated with potassium iodide in large doses because, on clinical grounds, the disease was tentatively attributed to a fungus infection. Though the improvement may have been purely fortuitous, potassium iodide might be worth another trial

Pulmonary alveolar proteinosis thus presents many problems, some of which may be solved by the detection of more cases and a detailed evaluation of the occupational and other possible ætiological factors Diagnosis can be established with certainty only by lung biopsy—a procedure which would be regarded by many as a rather drastic form of investigation in what may at first appear to be a relatively mild complaint As, however, the eventual prognosis is probably decidedly bad, subjection to lung biopsy is fully justifiable in cases with the clinical and radiological findings described

I wish to express my thanks to Dr S B Benton, the physician in charge of the case, Mr J S A Linton, thoracic surgeon, Dr C H. Wood, radiologist, and Dr J M Forrester, general practitioner, all of whom have been most cooperative in allowing me to make use of their records I am indebted to Mr E S McLeod for the photographs

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Addendum

The patient died in Sheffield Royal Hospital on April 25 The postmortem studies have not yet been completed, but I am indebted to Dr L Wolman, who performed the examination, for the preliminary information that death was due to multiple metastatic cerebral abscesses secondary to infection in relation to the pulmonary alveolar proteinosis Up to the time when cerebral symptoms developed there had been no significant clinical or radiological change in the patient's pulmonary state

PULMONARY ALVEOLAR PROTEINOSIS

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Pulmonary alveolar proteinosis was first described by Rosen et al (1958), who collected 27 cases from various sources over five years Since then 9 further cases have been reported, 8 of them from America (Friedman and Strickland 1958, Lull et al 1959, McDowell et al 1959, Moertel et al 1959, Siercacki et al 1959, Carlson and Mason 1960) 2 of the original cases have been described in greater detail (Carabasi and Barta 1959, Payseur et al 1958) Although clinical and pathological studies have been very full, the cause and appropriate treatment are still unknown. In view of the diagnostic difficulties, we record the following case

Case-report

A man, aged 21, had worked as a grocery-shop assistant, gardener, and wool packer He had had severe acne and seborrhœa since puberty, and was treated with superficial X-rays and ultraviolet light with moderate improvement. At the age of 16 he developed progressive lymphœdema of his right leg and genitalia, and in June, 1957, the preputial œdema necessitated circumcision At this time his hæmoglobin was 93% In the early part of 1958 aplastic anæmia was discovered and he was referred to Dr J F Wilkinson in the hæmatology department of the Manchester Royal Infirmary

The patient was a pale youth, apyrexial but ill-looking, with severe cicatrising acne on his face, neck, and shoulders The right leg and thigh, and the genitalia were grossly œdematous, and his left foot showed slight œdema In the left scrotoperineal fold was a superficial sinus discharging serosanguineous fluid, which had appeared two months previously The lymph-nodes were not enlarged The blood-pressure, cardiovascular system, and chest were normal

Investigations —Hæmoglobin 7 6 g per 100 ml , red-cell count 2,482,000 per c mm , colour-index 1 02, white-cell count 3200 per c mm (polymorphs 65%, lymphocytes 28%, monocytes 2%, eosinophils 3%, and basophils 2%), platelet-count 65,000 per c mm , reticulocytes less than 1% Sternal marrow was hypoplastic with no abnormal cells (Dr M C G Israëls) Coombs test negative Blood Wassermann and Kahn reactions negative Mantoux test at 1/100 negative Serum-albumin 3 5 g per 100 ml , serum-globulin 2 7 g per 100 ml , serum-bilirubin 0 4 mg per 100 ml , thymol-turbidity 1 unit, alkaline phosphatase 9 0 King-Armstrong units per 100 ml , blood-urea 24 mg per 100 ml Culture of discharge from sinus sterile Chest radiograph normal Radiographs of pelvic bones and of soft tissues of right thigh normal

Diagnosis and Treatment

The diagnosis was clearly aplastic anæmia The ætiology was uncertain as he had no history of exposure to marrow-depressing drugs, and the total dose of X-radiation, given five years before, seemed too small to be responsible He was treated with prednisolone 60 mg daily and concentrated red-cell transfusions He improved considerably, and was discharged to the outpatient clinic For the following nine months he remained well on 15 mg of prednisolone daily, and a transfusion of 1 pint of concentrated red cells every three weeks

Readmissions to Hospital

In July, 1959, he developed pyrexia, without localising symptoms The fever settled after four days, but recurred three days later with rigors He was given tetracycline, but did not improve Two weeks later he had spasms of sharp pain in the left side of his chest He had no cough On admission to hospital, the only changes on examination were the pyrexia of 101°F, and the healing of the perineal sinus

Investigations —Hæmoglobin 10 7 g per 100 ml , white-cell count 8200 per c mm (polymorphs 60 5%, lymphocytes 8%, monocytes 1%, eosinophils 20%, and basophils 10 5%), platelets 140,000 per c mm Serum-albumin 3 3 g per 100 ml , serum-globulin 3 1 g per 100 ml , serum-bilirubin 0 5 mg per 100 ml , thymol-turbidity 3 8 units, alkaline phosphatase 6 K A units per 100 ml Blood, urine, and sputum cultures sterile Widal agglutination tests negative Chest radiograph normal (fig 1)

Next day the patient's temperature returned to normal and he felt well He was discharged from hospital, but he had several short febrile episodes, and he required more frequent transfusions to maintain his hæmoglobin During September he had increasing exertional dyspnœa, and right-sided pleuritic pain and pyrexia developed He was readmitted in October

He was then dyspnœic at rest, and his temperature was 102 6°F There were crepitations at both lung bases, but no pleural friction rub could be heard

Investigations —Hæmoglobin 7 6 g per 100 ml , red-cell count 3,283,000 per c mm , colour-index 0 75, white-cell count 6400 per c mm (polymorphs 49%, lymphocytes 8%, monocytes 2%, eosinophils 35%, and basophils 6%), platelets 94,000 per c mm Sternal-marrow biopsy showed an active normal marrow (Dr Israëls) Serum-sodium 135 mEq per litre, potassium 4 4 mEq per litre, chloride 92 mEq per litre, calcium 9 8 mg per 100 ml , inorganic phosphate 3 75 mg per 100 ml Serum-albumin 2 7 g per 100 ml , serum-globulin 2 9 g per 100 ml , serum-bilirubin 0 4 mg per 100 ml , thymol-turbidity 2 8 units, alkaline phosphatase 8 K -A units per 100 ml , blood-urea 27 mg per 100 ml Lupus-erythematosus cells not present, Widal reaction negative, brucella agglutinations negative, blood and urine cultures negative Sputum-culture yielded a few colonies of a hæmolytic streptococcus, *Staphylococcus pyogenes*, and *Candida albicans* Complement-fixation tests for influenza A, B, and C, adenovirus, psittacosis, lymphogranuloma venereum, and Q fever were negative Chest radiographs showed diffuse cloudy opacities extending from both hila, but sparing the periphery—an appearance suggesting pulmonary œdema (fig 2) Electrocardiograms showed non-specific T-wave inversion in precordial leads

He became progressively more dyspnœic and he was intermittently cyanosed He continued to complain of pleuritic pains, variable in site and degree The chest signs did not alter, but serial radiographs showed extension of the opacity to the periphery of the lung fields Because he had had steroids for a year he was treated empirically with antibiotics, though no infective cause for his fever was found He was given successively tetracycline, streptomycin, and chloramphenicol A low-salt diet and chlorothiazide produced no diuresis At the end of December he became acutely dyspnœic and died within a few hours

Necropsy Findings

The body was thin, with extensive scarring of the face and upper trunk consistent with healed acne, and with several seborrhœic warts on the dorsum of the hands The right leg and genitals were œdematous, and there were some raised pink nodules, about 4 mm across, on the buttocks and genitals

The skull, dura, venous sinuses, meninges, cerebral blood-vessels, and pituitary gland showed no significant lesions The brain weighed 1410 g and appeared normal on section The teeth, gums, tongue, pharynx, œsophagus, and thyroid were normal macroscopically The heart weighed 240 g , the pericardium, myocardium, endocardium, valves, and chambers appeared normal, and there was no detectable atheroma of the coronary arteries The right pleural cavity contained 240 ml of cloudy orange fluid, and the pleuræ of both lungs were lightly coated with a fibrinopurulent exudate There was mucopus in the trachea and both main bronchi Both lungs were abnormally heavy, the right weighing 1190 g and the left 1310 g On section, the lung tissue was uniformly firm and greyish white, appearing completely airless apart from an occasional small group of aerated alveoli The hilar nodes were not enlarged

The peritoneal cavity, the stomach, and the intestines appeared healthy The liver weighed 1620 g and showed a little patchy pallor on section The gallbladder, bile-ducts, pancreas, and adrenals were normal macroscopically The spleen weighed 120 g and showed a small subcapsular infarct The kidneys each weighed 120 g , their subcapsular and cut surfaces appeared normal The ureters, bladder, and prostate were normal, the inferior vena cava, and the right iliac and femoral veins showed no thrombosis or other lesion The sternal and ver-

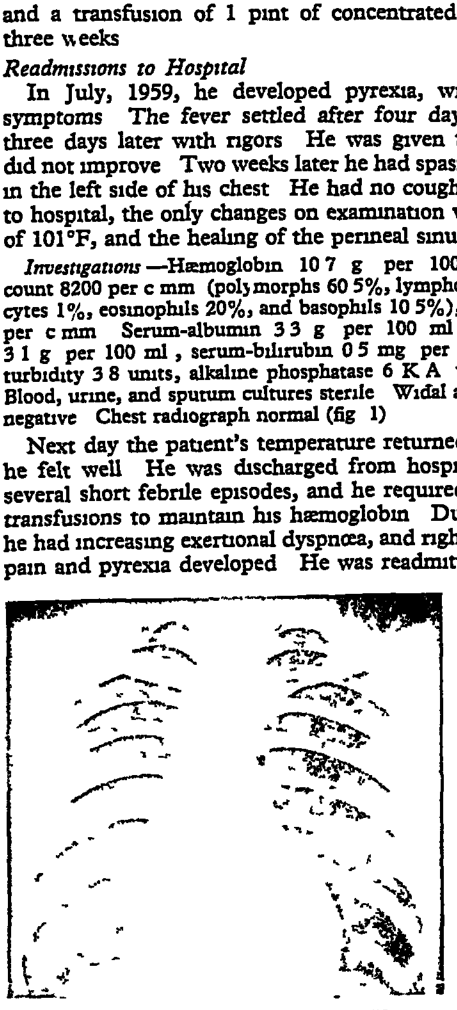

Fig 1—Normal chest X-ray (July, 1959)

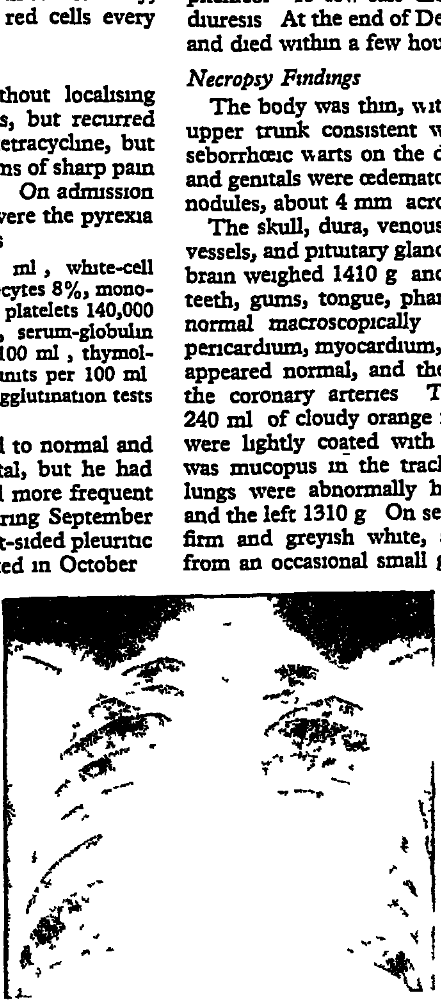

Fig 2—Chest X-ray on admission (October, 1959)

tebral marrow appeared normal, a little red marrow was mixed with the fat in the midshaft of the femur.

Histology

The histological appearances of the lungs were in most ways typical of alveolar proteinosis.

Nearly all the alveoli, bronchioles, and small bronchi were full of a granular eosinophilic material which was strongly periodic-acid/Schiff (P.A.S.) positive, and which contained acicular clefts. The lining alveolar cells had swollen and proliferated to form a continuous lining to most alveoli (figs 3 and 4). These cells were often vacuolated, and sometimes contained P.A.S.-positive granules. some large foamy cells lay freely in the intra-alveolar material, and occasionally more deeply staining laminated bodies, apparently the remnants of disrupted cells, could be seen. A few intra-alveolar red cells were present but no gross hæmorrhages. In frozen sections, the swollen intra-alveolar cells were seen to contain a great deal of sudanophilic material, and a large number of long thin birefringent crystals, which were not sudanophilic, corresponded to the acicular spaces seen in paraffin sections.

The alveolar walls showed moderate patchy fibrosis, which in general contained no inflammatory cells. In a few areas the alveolar contents had calcified in toto, apparently having shrunk to form a group of calcified, often laminated, bodies embedded in dense fibrous tissue. Occasionally the alveolar contents were reduced to a mass of crystals, which also became surrounded by fibrous tissue with loss of the alveolar structure. No pneumocystis organisms or other pathogens could be identified with Gram's stain, Jenner-Giemsa, or Gomori's methanamine-silver method. Superimposed on this general picture in a few parts of the lung there was a patchy nonspecific bronchopneumonia, and acute pleurisy was generalised. In the areas of bronchopneumonia the polymorphs appeared to phagocytose the abnormal material. A single microscopic abscess was packed with fungal hyphæ which resembled aspergillus rather than candida. The walls of the bronchi and the blood-vessels appeared normal. Only a very occasional eosinophil leucocyte was seen. The bronchial lymph-nodes did not contain abnormal material.

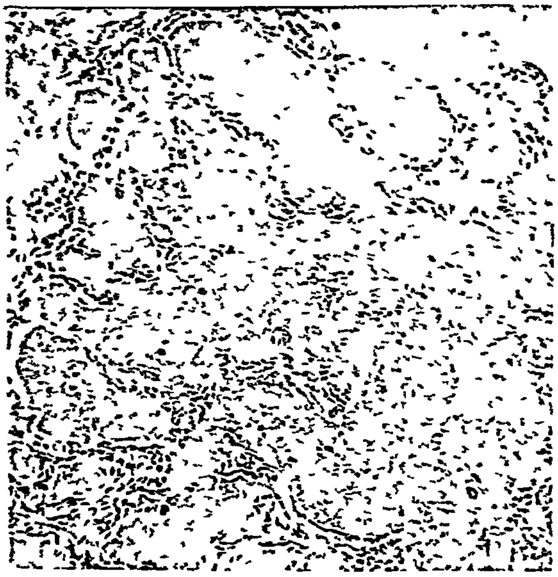

Fig 3—Photomicrograph of lung (× 110)

Sections from the thyroid, pituitary, brain, heart, kidney, and œsophagus were normal. The liver and spleen contained some hæmosiderin. The nodules on the buttocks showed only dermal fibrosis. Active erythropoiesis was seen in the femoral marrow. The testicular tubules were lined exclusively by Sertoli cells, and spermatogenesis was not visible.

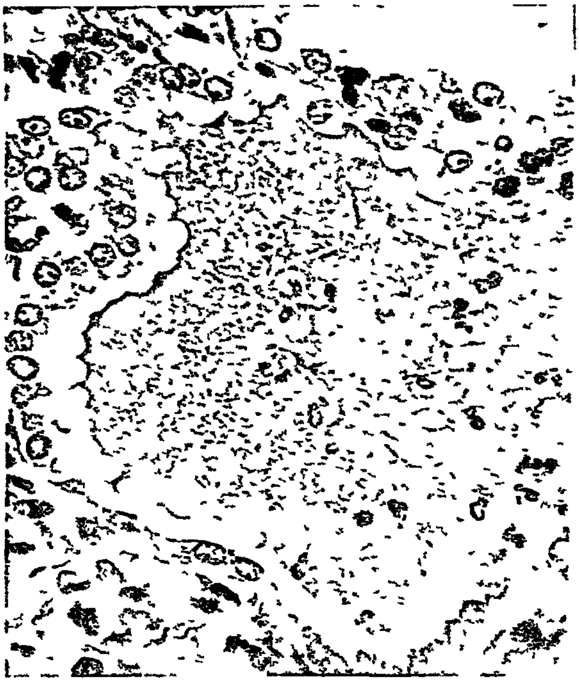

Fig 4—Photomicrograph of an alveolus (× 500)

Discussion

The cause of pulmonary alveolar proteinosis is unknown. No specific pathogens have been isolated. Though a few patients have been exposed to various dusts, most have not, nor do the lesions resemble those of the various pneumoconioses. In one case alveolar proteinosis developed two years after the successful treatment of pulmonary tuberculosis (Payseur et al. 1958). None of the previous cases have had aplastic anæmia, though 2 had severe acne (Rosen et al. 1958, Sieracki et al. 1959), and it seems that these conditions are unrelated to alveolar proteinosis. The nature of the intra-alveolar material is obscure. its staining reactions indicate a high content of carbohydrate, and it also contains about 20% fat (Rosen et al. 1958).

Clinically the disease is not very well defined. It seems to be about three times as common in men as in women, and it usually occurs in adults, though it has been reported in 2 children, aged $2\frac{1}{2}$ and 15 years. The symptoms vary. The commonest sequence is (as in our case) a febrile influenza-like illness with no localising features, followed by a symptom-free interval, and then by the onset of progressive dyspnœa associated with a productive cough, low-grade fever, chest pain, and loss of weight. Despite severe dyspnœa the physical signs are unimpressive. Scattered coarse or fine rales may be heard, but not a friction rub even in the presence of pleuritic pain. Cyanosis and finger-clubbing have been seen when the illness was severe. In one of Rosen's patients who had had the disease for four years evidence of right ventricular failure and pulmonary hypertension was confirmed by cardiac catheterisation.

The radiographic changes, characteristic though not pathognomonic, comprise fine diffuse perihilar shadowing, which may extend to the periphery as the disease progresses. The mediastinal lymph-nodes are not enlarged. The initial radiological diagnoses have included pulmonary œdema, sarcoidosis without glandular enlargement, pneumoconiosis, and pulmonary infection, particularly viral or fungal

The hæmoglobin level is often high, which is unusual in a febrile wasting illness, but this may be part of a secondary polycythæmia Otherwise no constant hæmatological or biochemical abnormality has been found Only three earlier reports have included a full differential leucocyte-count, but there has been no mention of eosinophilia, which was such a striking feature of our patient's last illness Pulmonary function tests show no characteristic abnormalities Severe cases have evidence of an alveolar-capillary block

Pathologically the most difficult differential diagnosis is from *Pneumocystis carinii* pneumonia Although typically a disease of infants, this has been reported in adults, usually associated with cytomegalic inclusion disease or a reticulosis (Hamperl 1956, Mur 1959, Symmers 1960) As Hamperl (1957) has pointed out, the characteristic plasma-cell infiltrate may be absent, when the picture may closely resemble that of alveolar proteinosis, with epithelialised alveoli containing P A S -positive masses The organism can usually be readily stained with Gram, Giemsa, or Gomori's methanamine-silver method, and the birefringent crystals (or acicular clefts) have not, to our knowledge, been reported in pneumocystis pneumonia except in the first case of Reye and ten Seldam (1956) But this child was $2^1/_2$ years old (exceptionally old for pneumocystis), plasma-cells were scarce, and only a very occasional organism could be identified otherwise the appearances were typical of alveolar proteinosis, which in retrospect may have been the basic disease

Pulmonary fibrosis has been recorded previously only twice in a man in whom the biopsy was taken four years after illness started, and at necropsy in a patient dying fourteen months after the first symptom So far as we know, calcification has not been previously recorded Although the laminated calcified bodies resembled superficially those of microlithiasis alveolaris pulmonum, they were not birefringent, and were always seen in disorganised fibrosed alveoli, so an ætiological relation between the two conditions is unlikely The failure of spermatogenesis in our case could not be satisfactorily explained œstrogens had not been given, and the skin near the testes had not been irradiated

The prognosis is very variable None of the original series had been observed longer than five years, but during that time 8 died, all with respiratory insufficiency, which was associated in 3 cases with a fungal infection 5 (1 of whom showed complete radiographic resolution) improved over periods of nine months to five years No effective treatment is known Neither antibiotics nor steroids have been of any benefit except in the case reported by Moertel et al (1959), which improved while prednisolone was given In fact simultaneous broad-spectrum antibiotics and corticosteroids may well predispose to secondary fungal infection, as in our case In the only 2 cases in which it has been given, potassium iodide may have helped in 1 it was used during the prodromal illness (Lull et al 1959) and in the other in the fully developed illness, when the very high dosage of 8 g daily was given, with complete recovery over the next few months (McDowell et al 1959)

In only 1 case (Carlson and Mason 1960) has alveolar proteinosis been diagnosed before thoracotomy or necropsy Sections of fixed sputum showed laminated bodies and acicular clefts in granular material, with the typical staining reactions Diagnosis from fresh sputum may be possible Fat-laden macrophages, which are so striking a feature of many cases, are common in several other pulmonary conditions (Waddell et al 1949) and have been found in the sputum in a high proportion of cases of bronchial carcinoma (Hammer and Rohrbach 1959) The birefringent crystals, on the other hand, are probably specific for alveolar proteinosis, and might be detectable with polarised light in unfixed material

Summary

A 21-year-old man with aplastic anæmia, progressive lymphœdema, and severe acne developed fatal pulmonary alveolar proteinosis with much eosinophilia At necropsy the typical changes of this condition were found—namely, firm greyish-white airless lung tissue—with, in addition, patchy fibrosis and calcification

We are grateful to Dr J F Wilkinson for permission to publish this case-report, to Dr M C G Israels for reports on the bone-marrow, to Prof A C P Campbell and Dr George Williams for advice, and to Dr R Ollerenshaw, of the department of medical illustration, and Mr N Mowat for preparing the figures

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Preliminary Communication

SERUM THAT DISTINGUISHES OLD CELLS

SEROLOGICAL DIFFERENCE BETWEEN OLD AND YOUNG CELLS

VARIOUS experiments have been done to determine the life-span of erythrocytes, but very little is known concerning the mechanism by which aged cells are removed from the circulation, though antigenic changes in the red-cell surface on storage, revealed by an increased erythrophagocytic index [1] and by agglutination,[2] have been described In the serum described here it was found that a change in the red-cell surface takes place on ageing in vivo as well as in vitro

SEROLOGICAL FINDINGS

The serum of a married woman, aged 71, with anæmia secondary to Hodgkin's disease, was referred to us owing to difficulty in the cross-matching test Her hæmoglobin was 7 3 g per 100 ml , red blood-cells 2,700,000 per c mm , and she had received no recent transfusion, but had been transfused eighteen months previously during a splenectomy The patient died early in the investigation and this unfortunately prevented study of the clinical effects of the agglutinating property

Examination of her blood showed that she was group O, R_2r, Ns, P−, Lu(a−), K−, Le(a−b−), Fy(a+), Jk(a+), and that her serum agglutinated all of a wide range of test cells, though these tests, together with a number of absorptions, failed to disclose any specific blood-group antibody It was noticed, however, that stored cells gave stronger results than freshly collected ones, while cells preserved in glycerin citrate at −20°C

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[1] Moskowitz, M *Nature, Lond* 1955, 175, 595
[2] Jenkins, W J , Marsh, W L Personal communication

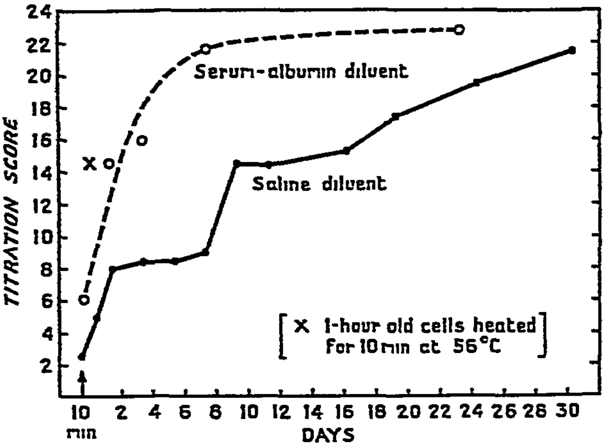

Fig 1—Effect of storage of red cells on strength of agglutination

were agglutinated more strongly still and further tests confirmed that the strength of the agglutination depended on the period of storage. The patient's serum agglutinated her own cells only feebly when they were fresh but more strongly after storage.

The agglutinin was most strongly active at 37°C against cells suspended in serum-albumin, though it also agglutinated cells in saline suspension, strongly at 37°C and less strongly at 16°C In the indirect Coombs test, the cells were equally strongly agglutinated following washing, whether anti-γ-globulin, anti-non-γ-globulin, or saline was added to them, but the direct Coombs test using the patient's own fresh cells was negative. Further testing was carried out mainly by the saline-agglutination and serum-albumin techniques at 37°C

The effect of storage on the strength of the agglutination is illustrated by fig 1, which shows the results of an experiment in which a sample of blood was taken from a normal healthy donor into small bottles containing A.C.D anticoagulant. These were stored at 4°C for various periods, following which the cells were washed and tested in saline and in serum-albumin suspensions against a series of doubling dilutions of the patient's serum at 37°C. The agglutination score was plotted against time of storage. The score given by fresh cells artificially aged by heating at 56°C for 10 minutes is also shown and is equivalent to that given by the same cells stored for 14 days at 4°C Similar results were obtained when cells were stored in E.D.T.A., heparin, and as defibrinated blood.

The agglutinating property could be removed from the serum by absorption with stored cells, though we were unable to recover it by elution at 56°C The property was not affected by heating the serum at 56°C for half an hour, nor by the addition of H-secretor or non-secretor saliva No reversal of agglutination took place on incubation at 37°C for 20 hours, and when cells agglutinated by the serum were washed repeatedly in saline they remained agglutinated, showing that the agglutinating factor was firmly attached to them.

Two interesting features were that the appearance of the agglutination was unusual, only some of the cells being agglutinated and that the reaction was so rapid that strong agglutination could be obtained after only 2 minutes' incubation at 37°C followed by centrifugation

The patient's serum contained only 10 units per ml of complement (normal range 85–100) By treating stored cells with inactivated patient's serum for very brief periods followed by normal fresh serum and then testing with anti-non-γ-globulin fixation of complement could be demonstrated.

Treatment of saline suspensions of red cells with alumina, with 1·03 *M* NaCl, or by multiple washings, all result in pronounced losses of lipids from the red-cell surface, similar to those which take place on storage,[3] but none of these treatments had any effect on the strength of the agglutination in this case

A sample of blood from a normal donor freshly collected into A.C.D., was separated by the differential centrifugation method of Constandoulakis and Kay[4] so as to give a high percentage of young cells in one portion and a high percentage of aged cells in a second portion It was found that the proportion of agglutinated cells was small in the first portion and large in the second, showing that the change in the red-cell surface, which is detected by this serum, takes place in vivo, though possibly at a slower rate than in vitro (see fig 2)

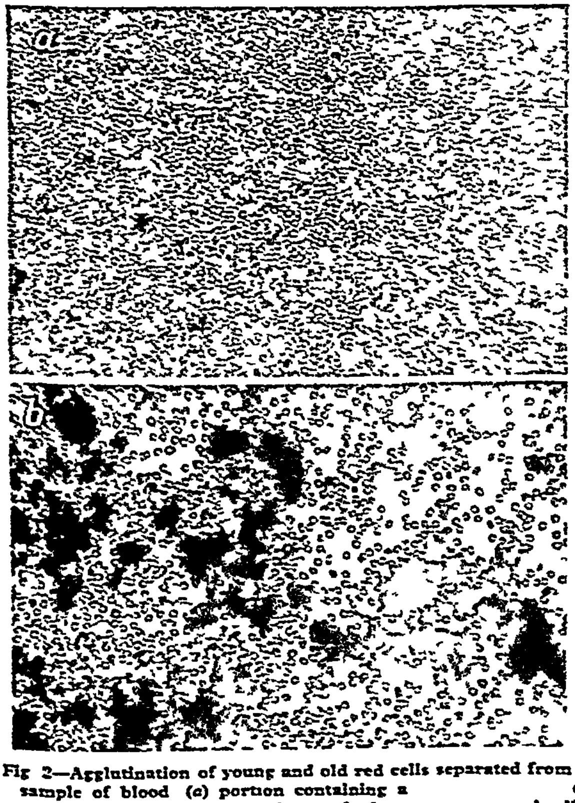

Fig 2—Agglutination of young and old red cells separated from a sample of blood (a) portion containing a of young cells (b) portion containing a high cells.

DISCUSSION

The reactions of this serum were not easy to interpret. When a fresh sample of the patient's blood was examined it was at first thought, in view of the weak result with her own cells, that a blood-group antibody of some kind was present. Using an older sample of the patient's cells, however the agglutination was a good deal stronger and the pattern of results obtained resembled that given by a warm autoagglutinin, such as is sometimes seen in cases of acquired hæmolytic anæmia Indeed, it may well be that there is a relationship with such cases

On further testing it became clear that we were not dealing with a specific blood-group antibody but with an agglutinin active against stored cells The nature of this agglutinin is unknown. If it is an antibody the source of the antigenic stimulus is obscure, and further experiments will be necessary in other cases to determine its nature

The appearance of a mixed agglutination, with both agglutinated and free cells present, was ascribed to the presence of cells of different ages, and this supposition was confirmed by the differential centrifugation experiment.

A change of some kind in the red-cell surface occurring on storage and also on ageing in the circulation, could be

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3 Lovelock, J E *Nature Lond* 1954 173, 659
4 Constandoulakis, M. Kay H. E. M *J clin. Path* 1959, 13,

demonstrated by means of this serum, and it is interesting to speculate as to what part, if any, this change plays in the normal process by which effete red cells are destroyed We do not know what part it played in the causation of the patient's anæmia, though it seems possible that the feeble nature of the agglutination of a fresh sample of the patient's cells by her own serum might have been due to an increased rate of elimination of aged cells from her circulation

We are indebted to Dr R M Fulton, Stepping Hill Hospital, Stockport, for the clinical details of this case

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Reviews of Books

Selected Papers

SIR GEOFFREY JEFFERSON, C B E, M S, F R C P, F R C S, F R S, emeritus professor of neurosurgery, University of Manchester London Pitman Medical Publishing Co 1960 Pp 575 105*s*

THESE twenty-nine personally selected papers are representative of all that is best in Sir Geoffrey's writings During the past thirty years he has had few equals in the profession of surgery, either for the range of his interests and knowledge or for the philosophy of his thought The book is largely formed by original papers on the tentorial pressure cone, the chiasma and aneurysms, the pituitary, the cavernous sinuses, the frontal lobes, and the problems of consciousness and its loss which have interested him for so long There are accounts of the lives, personalities, and works of some of the neurosurgically great of the past, among them Sir William Macewen, Sir Victor Horsley, and Harvey Cushing These sketches show the author's belief in the axiom that we cannot fully understand the present without knowing too the ancestry of today's ideas and today's achievements Some essays of a more general kind deal with philosophical questions and personal reminiscences, all essentially neurological in a wide sense Preference has been given in the main to papers published some years ago, making them more accessible to the younger generation But it is in no way a book of operative surgery

This writer of charm, wisdom, and unrivalled experience begins characteristically by meditating on the sources of knowledge and ends by reflecting "on being happy and liking it" This splendid book will fascinate neurologists, philosophers, and medical historians the like of it rarely comes our way

Modern Trends in Pathology

Editor DOUGLAS H COLLINS, O B E, M D, F R C P, professor of pathology, University of Sheffield London Butterworth 1959 Pp 460 65*s*

WHETHER one looks on it as a defect or as a merit, this book reflects not the trends but the crisis in modern pathology It is the crisis which animates much of the controversy about a pathologists' college, and its outcome may influence all branches of medical practice in this country for many years It has been brewing ever since pathology ceased to be synonymous with morbid anatomy, without, at the same time, acquiring a precise new meaning At least two-thirds of the volume will be outside any one reader's immediate interest The chapters, written by a galaxy of professors, range from such orthodox morbid anatomical subjects as rare and recently identified tumours (by Prof R A Willis) to the biochemical vagaries of 5-hydroxytryptamine, and from cancer in Africa (brilliantly surveyed by Prof J N D Davies) to occupational lung diseases they have not even in common such negative qualities as a comparative unconcern with bedside practice

To do justice to such a work a committee would have to review it The contributors set a very high standard and the same is expected from the reader Even chapters of wide "general" interest such as Sir Roy Cameron's on the injured cell and Prof R J V Pulvertaft's on the examination of pathological tissues on the fresh state are no light reading they provide food for active minds, not stimulants for the sluggish The more specialised sections may provoke some to wonder what modern pathology does not include Are we witnessing the beginning or the end of Virchow's dream—pathology, the mirror of all medicine and surgery?

Fluid Balance in Obstetrics

PHILIP RHODES, M B, F R C S, M R C O G, consultant obstetrician and gynæcologist, St Thomas's Hospital, London London Lloyd-Luke (Medical Books) 1960 Pp 169 25*s*

THERE are several excellent short books on fluid balance in surgery, and a similar volume dealing with fluid balance in obstetrics is welcome The author is a practising obstetrician, which gives him the advantage of direct familiarity with the specific clinical situations, perhaps at the expense of really expert knowledge of fluid balance Unless the author has been unduly modest, the references at the end of each chapter seem to indicate that he has not contributed original work in this field, but he has been diligent in surveying the literature In some chapters indeed the resulting picture is a little confusing, notably in the account of eclampsia—admittedly not an easy subject to handle His own view emphasises the importance of "stress", and regards changes in fluid balance as secondary The book is well written, and easy to follow, and gives a good general account of fluid balance In places the recommendations are rather behind current practice—for example, the condemnation of mercurials because "they have to be given intravenously" (p 104), or the routine use of penicillin in anuria, and also the rather high water intake in that condition There are some quantitative errors aldosterone output is given in mg instead of µg (p 99) and the protein content of œdema fluid is given as "0 24 Gm per ml" (p 92) The author's intentions are so good that it may seem hard to criticise his performance, but in the next edition he might care to seek the collaboration of a specialist in the fluid-balance aspect

Massage, Manipulation, and Traction

EDITOR SIDNEY LICHT, M D, assistant clinical professor, Yale University School of Medicine New Haven, Conn Elizabeth Licht 1960 Pp 275 $10

THIS is the fifth volume in an American series devoted to a detailed examination of the techniques of physical medicine Previous titles were concerned with such agencies as heat, exercise, and electrical energy this one deals with what is probably the most venerable of all the methods with which man has tried to heal his fellows

It has also proved the most contentious, and, perhaps for this reason, the book has a slightly apologetic tone throughout Yet it is, in fact, a carefully reasoned and exact study of a subject where precision is notoriously elusive Even those who are unenthusiastic about manipulative treatments will find a certain fascination in its pages, for they contain a very exhaustive survey of the early history of physical medicine (with over 170 references), and a description of the 'Syncardon' which amplifies the radial pulse and uses it to trigger synchronous pressure waves applied to the lower limbs in the treatment of obliterative vascular disease

Hypnosis in Anæsthesiology

MILTON J MARMER, M D, M SC MED, chairman, department of anæsthesia, Cedars of Lebanon Hospital, Los Angeles, California Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1960 Pp 150 54*s*

AS a practising anæsthetist, Dr Marmer propounds the view that the surgical patient is best not told that hypnosis is to be attempted—not at any rate in the first place—but that an exercise in relaxation is to take place This is the sort of preoperative talk that any patient might expect, and it may occasionally lead to a trance state. As a thesis, however, it indicates that Dr. Marmer is interested in the value of suggestion as an adjunct to chemical anæsthesia, perhaps more so than in hypnosis as a substitute for it. He has written a practical account of the subject, describing in detail the methods of trance induction, and illustrating by case-reports its uses for various operations. This is a very fair account of the potential value of hypnosis to the anæsthetist.

Recent Advances in Cardiology (5th ed. London: J. & A. Churchill. 1960. Pp. 421. 45*s*.)—Ten years have elapsed since the previous edition of this well-known work, and cardiology has been completely reorientated by physiological investigations and cardiac surgery. The new edition is edited by Dr. Terence East and Dr. Curtis Bain. It may be questioned whether this volume, even though enlarged to the size of a small textbook, can do justice to this revolution, for it has to cover both common and rare diseases and give full references. Inevitably it has become difficult to read in places and sometimes difficult to understand. There is little room for the enunciation of general principles or for the clinical and physiological approach which has been perhaps the strength of British cardiology. The section on congenital heart-disease lacks the physiological approach and some statements are hard to follow (e.g., "The modern trend of thought is to link up the Roger type of ventricular septal defect with that included in the syndrome of Eisenmenger"). The inclusion of Roger's description of the systolic murmur in small ventricular septal defects is valuable and there is a very good section on acute and chronic rheumatic carditis. It is stated that the causes of cardiogenic syncope are well known and include complete heart-block, but complete heart-block does not produce syncope unless the ventricular pacemaker has failed, causing arrest, and arrest is not necessarily associated with complete heart-block. The systolic murmur in hypertension is ascribed to mitral regurgitation and the much commoner and unimportant aortic systolic murmur is not mentioned. Though this book is not altogether suitable for undergraduates or those training in cardiology, it is a very useful compilation of facts and references, and it is finely produced.

Current Therapy 1960 (Philadelphia and London: W. B. Saunders. Pp. 808. £4 4s.)—In the twelfth annual edition of this excellent work, edited by Dr. Howard F. Conn, the general layout and the subjects covered are much the same as last year, but many of the articles are by new authors. The whole range of general medicine is covered as well as dermatology and obstetrics and gynæcology. Only psychiatry is poorly represented, and in view of the ever-increasing use of drugs in this specialty the gap is surprising. The book is 27 pages longer than the last edition but the price is not increased. It remains extremely good value as a work of reference for the practitioner or the hospital library.

New and Nonofficial Drugs 1960 (Philadelphia: J. B. Lippincott. Pp. 768. 30*s*.)—This annual publication of the Council on Drugs of the American Medical Association is chiefly concerned with drugs generally available in the United States that have not been included in the *U.S. Pharmacopeia*, the *National Formulary*, or *New and Nonofficial Drugs* in the previous twenty years. It is a very valuable guide to pharmaceutical innovation and progress.

New Inventions

A CLINICAL THERMOMETER

THIS simple, accurate, and rapid thermometer for clinical use depends upon thermistors (negative-temperature-coefficient resistors) as heat-sensitive elements. The thermal ohmic change is measured by a very stable bridge circuit based on that originally developed by Phillips Laboratory (S.A.) Ltd.

The thermometer consists of a bridge circuit, meter-adjusting potentiometers for fine and coarse adjustment, and a 6-volt battery (fig. 1). The negative-temperature-coefficient resistors are connected to the circuit by extension leads and telephone jack plugs. Three small shunt resistors of 1·5 kilohms are inserted in the jacks as shown, to protect the meter if one or more thermometers are taken in or out of circuit while the instrument is switched on.

When the temperature of the resistor rises or falls the bridge circuit is unbalanced, giving a meter deflection proportional to the change of temperature.

Fig. 2 shows the thermometer built in the department. The instrument was designed specifically as a clinical thermometer and is used for determining skin, rectal, and intra-abdominal temperatures, especially during hypothermia. (The thermometer can be enclosed in a thin plastic sheath.) It is also used during laboratory experiments with animals.

All three temperature-sensitive elements may be used simultaneously: a three-pole switch selects the one from which the reading is to be made. The range of temperature is from 15°C to 40°C with an accuracy of ±0·1–0·25°C. The equipment costs between £10 and £12.

Thanks are due to Messrs. Phillips Laboratory (S.A.) Ltd. for permission to modify the original circuit.

Department of Surgery,
University of Natal,
South Africa

C. J. LOCKETT
D.E.E. Lond., Technician

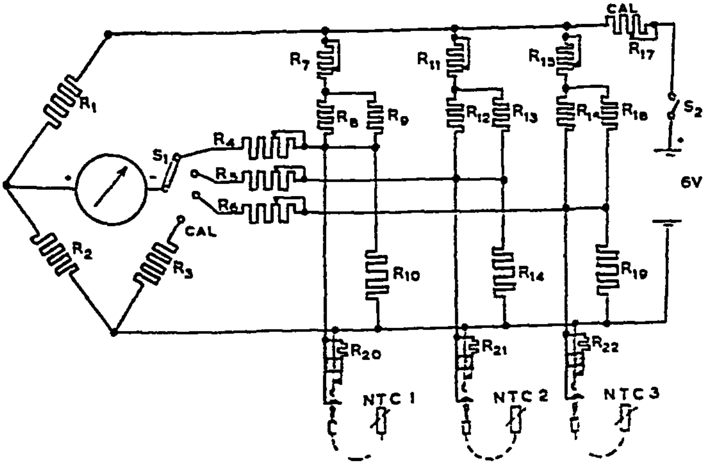
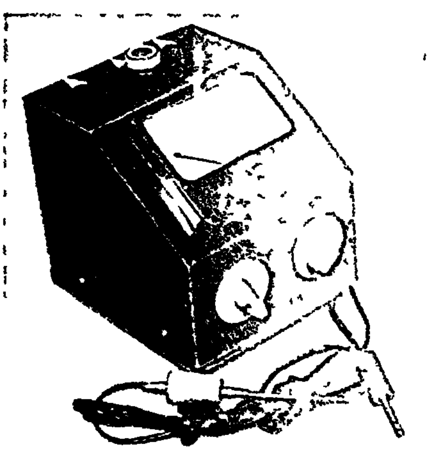


Fig. 1—Circuit diagram. N.T.C. = negative temperature coefficient resistors.



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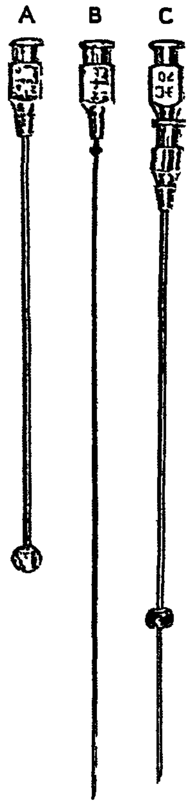
GUIDE FOR PUDENDAL NERVE BLOCK



PUDENDAL nerve block by the transvaginal method is gaining increasing support from obstetricians throughout the world The method has already been described by Huntingford [1] In practice it helps to use a guide which prevents the needle from piercing the operator's glove or the vaginal wall during introduction

Such guides have been described in the past two years by Kohl [2] and Velarde [3] Our guide has the virtue of simplicity, being easy to make, to clean, and to sterilise It has been in use since March, 1957, and has been received enthusiastically by our colleagues

The guide is made by tightly fixing a metal bead to the sharp end of a 4-in no 17 needle The protruding sharp end is then ground off (see figure A) With the index finger the beaded end of the guide can be easily placed in position beneath the tip of the ischial spine A 5-in no 20 needle (B) is then passed through the guide (C) until it is felt to pierce the vaginal wall The anæsthetic solution can thus be accurately placed close to the pudendal nerve

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M D
MICHAEL B FLANAGAN
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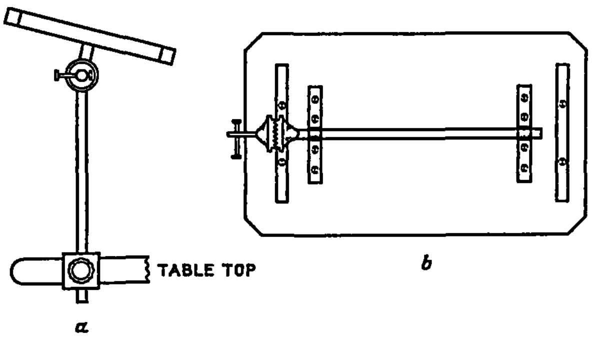
A SCREEN FOR USE DURING THORACIC OPERATIONS

IN the past, when patients have undergone thoracic surgery in the lateral position, I have found difficulty in maintaining adequate access to the face, and also in keeping the assistants' elbows away from the face and neck

All these difficulties have been overcome by a special screen (see figure) The side view (*a*) shows that it comprises a rectangle of laminated timber, 10 × 22 in, faced all round with 'Formica' This rectangle is attached to a serrated-face knuckle joint, giving a rigid fore-and-aft tilt of about 270° The pillar on which the knuckle joint is mounted is 20 in long, and is clamped to the side rail of the head section of the operating-table It may thus be raised or lowered, and moved forwards and backwards, as the occasion demands Because the screen is symmetrically mounted, it can be mounted with the pillar behind the patient's head in either lateral position, leaving unrestricted access to the face for manipulation of endotracheal tubes for suction, or for insertion of œsophageal tubes, bougies, or œsophagoscopes



The underside view (*b*) shows the attachment of the rectangular screen to the knuckle joint, and, at either end, flat spring clips for securing sterile towels When the towels have been placed under the clips, small 4-volt or 6-volt bulbs supplied by a transformer may be attached to the centre rod by 'Terry' clips

As well as its use for patients in the lateral position, the screen has been of value for neonates and infants in the supine position Our ear, nose, and throat surgeons have also used it as an instrument table when draped with sterile towels

This screen was made to my instructions by Chas F Thackray, Ltd, 10, Park Street, Leeds, 1

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NEW VAGINAL SPECULUM

IT is always difficult to expose the cervix after delivery because the vaginal walls tend to bulge inwards and obscure the view, even if one has an assistant Suture of a lateral laceration or of Duhrssen's incisions under direct vision is therefore sometimes impossible, but the speculum shown in figs 1 and 2 makes this easy even for the singlehanded obstetrician The instrument, which is a hybrid of Auvard's and Ferguson's vaginal specula and a proctoscope, has a diameter of 7 cm

It was made for me by Messrs Down Bros and Meyer & Phelps, Mitcham, Surrey

H P DUNN
F R C S, M R C O G,
F R A C S

Mater Misericordiæ Hospital,
Auckland, New Zealand

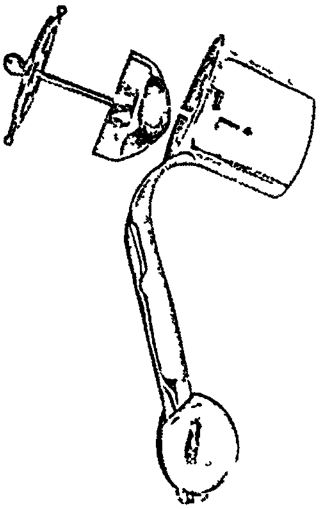

Fig 1—Lateral view of speculum, with obturator withdrawn

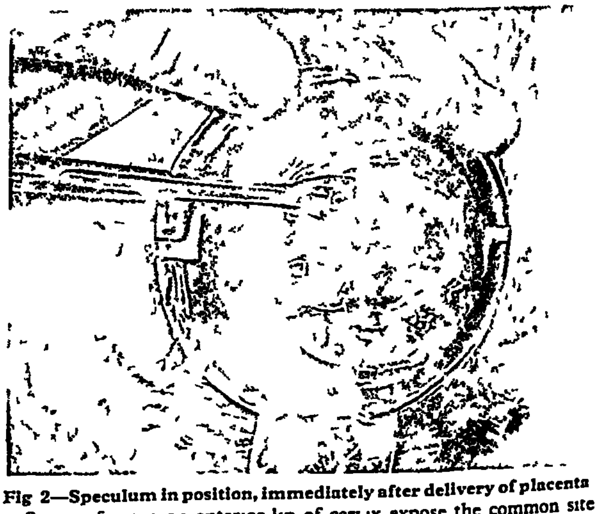

Fig 2—Speculum in position, immediately after delivery of placenta Sponge forceps on anterior lip of cervix expose the common site of lateral laceration There is adequate room to operate through it

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[1] Huntingford, P J *J Obstet Gynæc Brit Emp* 1959, 66, 26
[2] Kohl, G C *Obstet Gynæc* 1958, 11, 314
[3] Velarde, A *ibid* 1958, 10, 687

THE LANCET

LONDON 25 JUNE 1960

Bedsores of the Gut

HYPOSTATIC pneumonia has been called the bedsore of the lung—an ugly term which yet expresses the widespread feeling that common factors contribute to both. If "bedsore" is used in this comprehensive sense, we should probably include the acute ulcers of the gastrointestinal tract that sometimes arise under the same conditions as these lesions of skin and lung. For long these have aroused scant interest, and many clinicians still dismiss them as "terminal" changes. But our notions of changes that can properly be called terminal should be altering. Even in seemingly moribund patients, maintaining vital processes for a few extra hours occasionally gives Nature a chance to reassert its powers or allows life-saving treatment to be applied. In such cases hope may be frustrated not by the disease which has brought the patient to death's door but by the secondary effects of what, for want of insight, we must describe as a state of lowered vitality. The gravest manifestations of this include the breakdown of protective epithelia—whether of skin, bronchial tree, or gastrointestinal tract.

DALGAARD[1] has reviewed, in a series of 2317 necropsies, 208 cases of acute and 177 cases of chronic gastrointestinal ulcers. 70 of the acute ulcers—or, as DALGAARD prefers to call them, malacias—were associated with cerebrovascular lesions. These included subarachnoid and intracerebral hæmorrhages and thromboses, and the underlying diseases varied from essential hypertension to polycystic kidneys, leukæmia, and Hodgkin's disease. Two of DALGAARD's observations merit special attention. First, though these patients were already dying from intracranial lesions, the gut complications alone could have killed them. Secondly, despite microscopic evidence that these complications had begun several hours or even days before death, none had been diagnosed during life. The concentration of the lesions in the œsophagus, stomach, and duodenum suggests that chemical irritation played a part similar to that of mechanical pressure in the causation of skin sores, but these parts of the gastrointestinal tract are more thoroughly scrutinised at routine postmortem examinations than the distal segments, and it is certainly possible that similar lesions are distributed along its entire length.

Ever since CUSHING's[2] impressive account of acute duodenal ulceration following neurosurgical operations, a link between diseases of the central nervous system and of the gastrointestinal tract has been widely accepted[3], but how direct this relation may be is still far from clear. More than a hundred years ago ROKITANSKY[4] pointed out that acute gastrointestinal erosions are a common necropsy finding in diverse illnesses—"poisonings, chlorosis, cerebral diseases, eclampsia, burns, trauma, local infiltration, infection, and general sepsis"—and BRINTON[5] suggested in 1864 that "these [gastrointestinal] lesions complicate different illnesses in proportion more akin to their known frequency than to any other circumstance". We have certainly never been able to define, either anatomically or functionally, "ulcerogenic" loci in the central nervous system. In the 1930s BALO and other workers sought to demonstrate that damage to certain vasomotor centres in the midbrain could initiate vascular changes in the gastric mucosa, but similar lesions were later produced by experimental intracranial trauma in which the midbrain was safeguarded.[6–8] Support for BRINTON's view has come from a series of new causes which the passing decades have added to ROKITANSKY's list. Two world wars have introduced us to air-raid, frostbite, trench, and famine ulcers—and to the acute ulcers of the bomb-victims of Hiroshima and Nagasaki. In 1867 one of BILLROTH's first thyroidectomy patients died from massive duodenal hæmorrhage on the fifth postoperative day. Today no organ of the body remains surgically unexplored—and, whatever the organ, postoperative acute ulcer occasionally ensues. ROGER[8] has reported from Hungary three cases of gunshot wound admitted to a Budapest general hospital in the fateful autumn of 1956: all three patients died, while recovering from their wounds, from massive gastroduodenal hæmorrhage or perforation. And (reflecting, perhaps, the diversity of 20th-century *conditions humaines*) SHIPP et al[9] have issued from Boston another warning against ulcers complicating the acute phase of myocardial infarction.

Despite such multiformity of underlying diseases, many clinicians and pathologists still believe that intracranial lesions carry an especial risk. STRASSMANN,[10] who studied the prevalence of peptic ulcers in 1400 medicolegal and mental-hospital necropsies, found that of 26 acute ulcers all but 2 were associated with intracranial hæmorrhage, and, though DALGAARD's material is not suited to statistical analysis, he believes that cerebral apoplexy is particularly liable to result in gut complications. Whether or not, on numerical grounds, "neurogenic" ulcers deserve a special niche, morphologically they are indistinguishable from other secondary gastrointestinal ulcers. Clinically, too, these lesions have at least one feature in common. Whether the primary disease has been a burn, multiple injuries, fulminating sepsis, snakebite, exposure, or a stroke, the patient is either in a state of shock or (more commonly) recovering from it—the term "shock" being used in its time-honoured sense rather than restricted to the effects of sudden or massive blood-loss

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[1] Dalgaard, J B *A.M.A Arch Path* 1960 28, 359

[2] Cushing, H *Surg Gynec Obstet* 1932, 55, 1

[3] See *Lancet*, 1955, i, 495

[4] von Rokitansky, C. Handbuch der speziellen pathologischen Anatomie, vol. 2 Vienna, 1842

[5] Brinton W Lectures on Diseases of the Stomach London 1864

[6] Baló, J *Acta morphol* 1951, 1, 167

[7] Baló, J *Zschr allg Path* 1958, 21, 561

[8] Roger, M *Orvosi Hetil* 1960 101, 663

[9] Shipp, J C. Sidel V W, Donaldson, R. M, Gray, S J *New Engl J Med* 1959 261, 222

[10] Strassmann G S *Beitr gerichtl Med* 1952, 19 162

The clinician need hardly concern himself with the vexed question whether hormonal or nervous irritants play the predominant rôle in the breakdown of gastro-intestinal mucosal resistance, but thought is certainly needed for devising a prophylactic regime Ignorant though we are about most ætiological factors which combine to produce bedsores and hypostatic pneumonia, we have at least, by trial and error, evolved preventive measures which succeed in a high proportion of cases However slender his chances of survival, the burned patient is still carefully positioned in bed, and bedsores, even in comatose victims of a stroke, are rightly regarded as a blot on the nursing care But mouthwashes and occasional enemas are the beginning, middle, and end of gastrointestinal nursing We should guard against acting on slender theoretical grounds, but should we not consider whether the withholding of food by mouth from ill, shocked, semicomatose, and comatose patients does not needlessly expose their gut mucosa to severe chemical irritation? Intravenous therapy can provide water, salt, and calories, but it cannot neutralise or dilute gastrointestinal enzymes, nor stimulate peristalsis Was there some sense, after all, in that much-maligned cup of hot sweet tea?

Neurology in Great Britain

MEDICAL specialties wax and wane for a variety of reasons Neurology in the United States, for example, held a high position until the first world war Then the rise of neurosurgery and the influence of HARVEY CUSHING's powerful personality made many people believe that anything a neurologist could do a neurosurgeon could do better, and neurosurgery added to its prestige by throwing new light upon many functions of the brain Simultaneously, by a kind of pincer movement psychoanalysis sought to remove much of the mind from the neurologist's province But now for some time American neurology has been getting its own back, partly by showing that there are many important problems which neither neurosurgery nor psychoanalysis can solve, and partly by doing something towards their solution American neurology owes its present thriving state to several factors, the most important of which are the close relationship between neurophysiology, neurochemistry, neuropathology, and clinical neurology, and the expenditure of a great deal of money on training and research The result is that any senior neurologist who wants to go on doing research can do so, and all promising young neurologists have the opportunity to work on research projects in the departments of senior neurologists who are research-minded

Dr DENIS BRINTON [1] in his presidential address to the neurological section of the Royal Society of Medicine was mainly concerned to stress the inadequacy of the number of neurological consultants in the Health Service for the needs of the country Things are somewhat better than they were, but the neurological service is still seriously understaffed There are still some areas with no neurological consultant, and many regional-board areas have no neurological senior registrar There, consultants have only untrained staff to assist them in their hospital work, and there is no-one but an already hardworked colleague to do the work of two at times of holiday or sickness It is often impossible for the provincial neurological consultant to get away for even half a day to attend a meeting in London What is the use of suggesting that such people ought to be doing research?

Research is the key to the status of neurology in this country, for no branch of medicine can retain the respect of its colleagues and rivals unless it is clearly advancing the boundaries of knowledge in its own sphere If British neurology was more evidently doing that it would not need to fear disparagement The long and distinguished tradition of neurology in this country is illustrated by the history of the National Hospital (which is celebrating its centenary this week), and there is no doubt that neurology still has as important contributions to make to medical science as any other specialty Yet in 1959 England and Wales had only 67 neurologists As BRINTON shows, we have 1 neurologist for half a million of the population in the Metropolitan area, and 1 per million in the Provinces Neurological research can no longer be done by the individual clinician in his spare time Yet the number of whole-time research-workers in neurology is very small, and is not increasing The Health Service gives no encouragement to the clinician who wants to continue to devote part of his time to research In any case there are not the laboratories or technicians to make possible the expansion of research Moreover, though an active postgraduate institute of neurology is essential it is not enough by itself there should be research facilities in every major neurological department It is sometimes said that neurology is suffering from lack of contact with general medicine BRINTON gives reasons for rejecting this view, and it is surely putting the cart before the horse to say that more interest in general medicine would lead to more research in neurology If neurology had adequate resources for research, its research would invade general medicine

No doubt neurologists must shoulder some of the blame for the present state of affairs, but by no means the whole The Minister of Health and the Secretary of State for Scotland are responsible for the welfare and progress of all branches of medicine in the Health Service, the Medical Research Council for research, and the universities for both research and teaching If British neurology is really in danger of losing the position of leadership it has occupied so long, this is at least partly because the medical profession and the public are content to have it so

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[1] *Proc R Soc med* 1960, 53, 261

The Harvest Mite

THE harvest mite or berry bug is generally regarded as insignificant—one of life's minor horrors, and uninteresting medically because it does not cause serious disease. Yet this mite—*Trombicula autumnalis*—is very widespread, and discomfort occasioned by infestation with it can be intense. Its common names suggest that it is a nuisance only of the countryside, but in towns and semirural areas many cases of trombiculosis may be misdiagnosed as heat spots, urticaria, erythema, or dermatitis.

The larva of *T. autumnalis* hatches in summer in the earth. It is six-legged, red, active, and only 0.2 mm. in size—that is to say, smaller than *Acarus scabiei* and hardly visible to the naked eye. Only this larval stage feeds on warm-blooded hosts; the adult mite lives in the ground throughout the winter, and the eggs are laid in the spring. The normal hosts of the larvæ are rabbits, smaller mammals such as rats and mice, and domestic animals. The larvæ are most numerous in dry summers, especially towards the autumn. They are most liable to be picked up in moist weedy places, on river banks, and in open fields and under and about fruit bushes and trees.[1] They are found also on lawns, in parks, and on golf-courses.

The free-moving larvæ make their way through gaps in clothing at ankles, wrists, or collar to the skin of the limbs and body. As they can travel surprisingly fast (at two feet a minute) over the skin,[2] they soon reach areas distant from the point of entry. The sites most commonly attacked are the ankles (mainly behind the malleoli), behind the knees, the groins, the intercrural and gluteal folds, the insides of the thighs, the waistline where clothing presses, the axillæ, the neck, and the shoulders—places where the skin is soft, thin, and moist. The larvæ feed by attaching themselves to the skin, injecting an irritant lytic fluid into the skin, and sucking the liquefied cell products. Larvæ are not easily found on the skin, because, having fed, they drop off and disappear. The lesion is at first a small weal, intensely itchy, which soon becomes a small papule. The itchiness often persists for days or even weeks with remissions; a papule which has become quiescent may be reactivated by being scratched or rubbed. Persons exposed to attack vary widely in their susceptibility to infestation and in their reaction to the toxic substance injected by the larva. Some people seem to be completely immune, while others are severely affected.[3] Allergy may partly determine the severity of the reaction, and repeated infestation may lead to hypersensitivity, which may pass off in time. Since the intense irritation induces the patient to scratch or rub the lesion, secondary infection may follow. Especially in children, a severe attack may produce constitutional symptoms.

In countries where trombiculid mites transmit serious disease, preventive measures have included clearing away surplus vegetation and treatment of the surface of the soil with powdered sulphur or with acaricides.[4] But much can be done by individuals to prevent access of the larvæ to the body surface. Application of dimethyl phthalate or dibutyl phthalate to ankles, wrists, and neck, and also perhaps to boot-tops, trouser turn-ups, sleeves, cuffs, and neckband, may be found effective if repeated every day or so. Benzyl benzoate, similarly applied, has also proved effective. More lasting prevention can be achieved by impregnating clothing with repellants. In the treatment of the lesions themselves, small dabs of an anti-histamine cream may relieve the itching.

Annotations

TORQUAY

DECISIONS about the Royal Commission's report having been taken at last month's special meeting,[5] the representative body of the British Medical Association may have been looking forward to an easy time at its annual meeting in Torquay last week. But there is an application of Parkinson's law to gatherings of this kind, and representatives soon found plenty to argue about, though they did not always have brand-new topics to stimulate them.

Drugs for Private Patients has always been a popular banner at representative meetings, and it was again greeted affectionately, seemingly in the confident hope that it was being paraded for the last time. The supply of drugs for private patients through the National Health Service was "a debt of honour owed by the Conservative Party", announced one standard-bearer. Surprisingly, however, there seemed to have been some backsliding here: last year the representative body threw up only one vote against N.H.S. drugs for private patients; this year no less than eleven dissented, and eleven there remained despite a recount and a rescrutiny, perhaps to dispel a suspicion that the *Lancet* cricket team had somehow got into the hall.

The meeting was unanimously indignant about the hospital building programme. The Government's proposed expenditure over the next five years was regarded as "totally inadequate", and the squalid and outdated state of large provincial hospitals must be remedied by a replacement policy of greater vigour and efficacy. Mr. H. H. Langston, chairman of the Central Consultants and Specialists Committee, referring to a *Times* suggestion[6] that there was a real danger of overbuilding hospitals, maintained that they had not demanded more beds, simply more up-to-date hospitals. To those who knew the hospitals it was clear that big gaps had to be remedied.

Members of the National Federation of Spiritual Healers should not, the meeting pronounced firmly, be allowed to conduct their practice in National Health Service wards.[7] The spiritualists were condemned as self-styled healers with no justification for the title. They had nothing in common with ministers of religion and their views and methods were entirely different. Of course, Mr. Langston added, the hospital patient had the right to ask whoever he liked to visit him, but should he wish to receive treatment from a spiritual healer it should be made plain beyond all doubt that he was the patient of a doctor of the hospital while he was in hospital, and no treatment of any sort could be allowed which was not directed and authorised by the doctor under whose care the patient was

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[1] Jones, W. B. *Parasitology*, 1950, 40, 1.
[2] Jenkins, D. W. *Amer. J. Hyg.* 1948, 48, 22, 36.
[3] Allington, H. V., Allington, R. R. *J. Amer. med. Ass.* 1954, 155, 240.
[4] Baker, E. W., Evans, T. M., Gould, D. J., Hull, W. B., Kegan, H. L. A Manual of Parasitic Mites of Medical or Economic Importance. National Pest Control Society, Inc., New York, 195[illegible].
[5] See *Lancet*, May 28, 1960, p. 1178.
[6] *Times*, June 16, 1960, p. 13.
[7] See *Lancet*, May 28, 1960, p. 1177.

The inquiries of the Public Health Laboratory Service's committee[8] on the sewage contamination of bathing beaches in England and Wales had suggested that "with the possible exception of a few æsthetically revolting beaches the risk to health of bathing in sewage-contaminated sea-water can, for all practical purposes, be ignored" Representatives pronounced themselves flabbergasted at the committee's complacency, and they sympathised with Dr W H N Angus when he said that the public was not going to be hoodwinked by medical statistics and pathological techniques when they waded into this fæcal flotsam The pollution of the Solent "sewer" was said to be equivalent to three gallons of sewage in a small swimming-pool, and the meeting was obviously more impressed by this comparison than by assurances that the committee's findings were reasonable

On Monday a helicopter brought the Duke of Edinburgh, the retiring president of the B M A, to join the meeting, and he inducted Sir Arthur Porritt as president for 1960–61

SYPHILIS AND THE PUBLIC HEALTH

THE decline of infectious syphilis in Western countries since the 1939–45 war is rightly claimed as highly satisfactory There can be little doubt that much of this success has been due to penicillin, which has proved a thoroughly effective and comparatively safe remedy Effective treatment, however, does not completely solve the problem of venereal infections—a fact of which the increase in gonorrhœa in the past few years has forcibly reminded us In this country the number of patients with infectious syphilis has continued to decline, and has now reached a lower level than any previously recorded The total number of patients with acquired syphilis of less than a year's duration attending the clinics in 1946[9] —the year of highest incidence after the late war—was 17,675, but by 1958 the total had fallen to 704[10] Probably few cases are treated elsewhere than at the clinics and therefore this low figure does not greatly underestimate the prevalence

The chief medical officer of the Ministry of Health, in his report for 1957,[11] remarked that it was hard to understand why the number of new cases of early infectious syphilis continued to fall despite the continuing rise in incidence of gonorrhœa He suggested that higher dosage of penicillin, now often given in a slow-release medium for the treatment of gonorrhœa, might in some cases be responsible for aborting incubating early syphilis Yet early syphilis is beginning to increase in some countries where the same factors may be presumed to operate The Expert Committee on Venereal Infections and Treponematoses of the World Health Organisation[12] stated that in the U S A infectious cases of syphilis increased by 15% in 1959 over the preceding year, the disease has, in fact, been on the increase since 1954, and syphilis in all its stages ranks fourth among notifiable diseases in the U S A In recent years increases have been reported also from Finland, France, Italy, and various areas in Africa

The remarkable outbreak of infectious syphilis in Maryland, described in last week's issue, in which recognition of a single case of syphilis led to the detection of 44 other previously untreated cases, shows that this condition can spread among the promiscuous with epidemic force One striking feature of this group of cases was the youth of the patients All but 4 were under 25 years of age and 25 were under 20, a girl of 13 being the youngest A joint statement from the U S A by the Association of State and Territorial Health Officers, the American Venereal Disease Association, and the American Social Health Association,[13] declares that venereal disease is increasing among teenagers and children From 1957 to 1958 the number of reported cases of infected children aged 10–14 increased from 2443 to 2793 (14 3%) and of those aged 15–19 from 44,864 to 49,909 (11 4%) Full details for 1959 are not yet known, but 29 States and 21 cities have already reported increases in early syphilis in young people aged 15–19, and 25 States and 43 cities have reported increases in gonorrhœa in the same age-group There have also been reports of an increase of both diseases among children aged 10–14

In a symposium at this year's Health Congress of the Royal Society of Health[14] it was stated that evidence collected from 147 clinics for venereal disease in England, Scotland, and Wales showed that new cases of gonorrhœa had increased by 13 8% in 1958 over the total for 1957 By far the biggest increase was in young people aged 18–19 We must be vigilant and continue to strengthen our measures for prevention and control of venereal infections There is, perhaps, one particular lesson to be learnt from the Maryland experience and from methods in the U S A generally the more assiduous the efforts to trace contacts, the larger the number of infected persons brought under treatment Nevertheless the techniques of contact tracing must conform to the outlook of the society in which they are applied, and it is doubtful whether the method of "cluster-testing", in which not only sex contacts of patients but many other friends and acquaintances who might conceivably have been exposed are investigated, would be acceptable here

ANGOR ANIMI AFTER AQUEOUS PROCAINE PENICILLIN

IN 1951 Batchelor et al[15] described 8 cases in which intramuscular injection of aqueous procaine penicillin was followed by an immediate reaction of which the most striking symptom was anxiety with a conviction of impending death Bjornberg and Selstram[16] have now recorded similar reactions in 33 patients A constant feature was a conviction of impending death or severe anxiety, and sensory disturbances, such as paræsthesiæ and tactile, visual, and auditory hallucinations, were common, with various degrees of mental confusion The acute episode lasted for from minutes to an hour, with exhaustion and anxiety persisting for a few days or occasionally longer There were no prominent somatic effects, no vasomotor collapse, and no allergic manifestations Similar but less severe reactions occurred with previous or subsequent injections in some of the patients

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[8] See *ibid* Jan 9, 1960, p 100

[9] Report of the Ministry of Health for the Year 1957 part II, appendix C, table B, p 281 H M Stationery Office, 1958

[10] Report of the Ministry of Health for the Year 1958 part II, appendix C, table B, p 253 H M Stationery Office, 1959

[11] Report of the Ministry of Health for the Year 1957 part II, p 70 H M Stationery Office, 1958

[12] W.H O document WHO/VDT/257, Oct. 30, 1959, p 27

[13] Today's V D Control Problem joint statement by Association of State and Territorial Health Officers American Venereal Disease Association, and American Social Health Association, February, 1960, p 16

[14] *Med Offr*, 1960, 103, 251

[15] Batchelor, R C L, Horne, G O, Rogerson, H L *Lancet*, 1951, ii, 195

[16] Björnberg, A, Selstram, J *Acta psychiat Kbh* 1960, 35, 129

The immediacy of the reaction, and the occasional complaint of a strange taste in the mouth, led both groups of workers to ascribe the reaction to accidental intravenous injection of the aqueous procaine penicillin This form of reaction is important both because of its alarming nature and its frequency it apparently develops in about 3 per 1000 injections,[15] and is eighteen times commoner [16] than anaphylactic reactions

HEARTBURN

HEARTBURN means to doctors, and to some patients, a burning pain felt anywhere between the xiphisternum and the neck, often worse on lying down and after food It is often associated with hiatus hernia, duodenal ulcer, or gallstones Heartburn is believed to arise in the œsophagus from the regurgitation of gastric contents There has been more discussion of how reflux is prevented [17] than of how it causes symptoms and of whether hiatus-hernia dyspepsia is due purely to œsophageal reflux

Muscular contraction or artificial distension of the lower part of the œsophagus causes pain similar to heartburn [18] So also does hydrochloric acid, either by direct action on an inflamed mucosa or by causing muscular spasm There is evidence that a hiatus hernia produces heartburn only when reflux œsophagitis develops Thus, heartburn is a feature of the commoner sliding hernia but not of the rarer paraœsophageal or rolling type [19] In hernia of the rolling type reflux cannot be demonstrated radiologically, but Donnelly [20] was able to show reflux in all sliding herniæ by a careful technique A few hiatus herniæ—mainly the large paraœsophageal ones—produce no dyspepsia at all,[21] so the hernia itself cannot be the cause of the pain

In a group of patients with indigestion, Phear [21] found no difference between the symptoms of those showing hiatus hernia with reflux and those in whom reflux alone was demonstrable Slight intermittent regurgitation is common, and no doubt only persistent reflux causes œsophagitis Even this may be harmless as in Allison's fortunate patient [19] Since childhood she had been able to swallow a toffee, sing a hymn, and then bring up the toffee to enjoy at leisure during the sermon, despite fifty years' indulgence in reflux she had no œsophagitis The degree of œsophagitis may depend on acid and pepsin levels in the œsophageal fluid, though typical reflux dyspepsia may occur with achlorhydria,[22] and heartburn cannot be correlated with hyperacidity [23]

Heartburn and angina pectoris are referred to similar areas, and the differential diagnosis between these conditions may be difficult Angina is typically a constricting or pressing sensation closely related to exercise or emotion and relieved by trinitrin The electrocardiogram (after exercise if necessary) is abnormal in 95% of cases [24] The pain of hiatus hernia, on the other hand, is worse after meals and on lying or stooping, it is relieved by alkali or belching and spreads to the back None of these features is completely specific Moreover, hiatus hernia and ischæmic heart-disease are each found in overweight patients beyond middle age, and both may be present together Most hiatus-hernia patients with angina have an abnormal electrocardiogram or other objective evidence of ischæmic heart-disease,[21] [25] and the improvement in angina after treatment of the hiatus hernia suggests that this disorder may precipitate anginal attacks [26] In laboratory animals distension of the œsophagus has been shown to decrease coronary blood-flow [27] Baylis et al,[28] however, did not find electrocardiographic evidence of myocardial ischæmia during distension of the lower œsophagus in patients with ischæmic heart-disease

Even more confusing is the severe, lengthy attack of central chest pain caused by a hiatus hernia but clinically indistinguishable from myocardial infarction [18] There may even be positional changes in the electrocardiogram suggesting posterior infarction, but fever, increases in serum-transaminase or erythrocyte sedimentation-rate, and leucocytosis are absent

In conclusion, then, the heartburn of a hiatus hernia is caused by œsophageal reflux, a hiatus hernia and angina are often associated, and the hiatus hernia may aggravate angina by reflex coronary vasoconstriction

THE OTHER FALLING SICKNESS

No more pleasing prospect could be held before the eyes of most clinicians than that of distinguishing a dangerous but curable condition from clinically similar disorders which are bound to lead to the patient's death Dramatic as it may sound, this is often the position with subdural hæmatomas, particularly of the chronic variety [29] A patient, usually elderly, is found to show unexpectedly rapid mental deterioration, or starts to fall repeatedly, or becomes drowsy, or is admitted to hospital with urinary retention The patient's memory of the recent past is so poor that he cannot recollect it if he has been significantly injured, or indeed if he has a severe headache Minor pupillary inequality, or minimal pyramidal signs, or papillœdema, or perhaps no neurological abnormality can be elicited But the pertinacious clinician seeks the radiologist's help or even surgical exploration, and is rewarded by finding one of the few reversible dementias in the book There is an ineluctable satisfaction in all this

And yet in this issue we print three papers which must give rise to some thoughtfulness In the first place, not all treated patients with subdural hæmatoma survive In the series of Mr McKissock and his colleagues (p 1365) the surgical mortality-rate was 6%, but all the fatal cases were in children or persons over the age of 50 in patients over 60 the mortality-rate was 12% Furthermore they find that of the 179 known survivors 29 (16%) remain partly or totally disabled Only 3 out of 4 remain well after the illness Of a small group of 11 cases described by Mr Davies (p 1369) 7 were confused postoperatively and 4 remained permanently so, in 1 case Korsakoff's psychosis developed a year later These grave reminders emphasise that while one factor in the development of subdural hæmatoma may be progressive friability of veins with increasing age, another is atrophy of the brain itself Compression or distortion results in

and cellular insufficiency, and iatrogenic or dehydration may precipitate permanent

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17 *Lancet*, April 16, 1960, p 862
18 Dickson, R C *Canad med Ass J* 1960, 82, 773
19 Allison, P R. *Surg Gynec Obstet* 1951, 92, 419
20 Donnelly, B *Brit J Radiol* 1953, 26, 441
21 Phear, D *Lancet*, 1957, i, 708
22 Alvarez, W C Introduction to Gastroenterology New York, 1948
23 Bennet, T I, Ryle, J A *Guy's Hosp Rep* 1921, 71, 286
24 Wood, P, McGregor, M., Whitaker, W *Brit Heart J* 1950, 12, 363
25 Master, A. M, Dack, S, Stone, J, Graham,
58, 428
26 Gilbert, N C *Bull N Y Acad Med* 1942,
27 Gilbert, W C, Leroy, G V, Fenn, G K.
28 Baylis, J H, Kauntze, R., Trounce, J
29 *Lancet*, 1959, i, 505

of the brain to expand may be countered by carefully washing the subdural space, by closing the wound with the head lowered as far as possible towards the floor, and by inserting intrathecal saline—perhaps repeatedly Nursing for the first few days with the head lowered is also advisable, as gravity is a potent force where pressures are low, and the sitting position is always dangerous in space-occupying lesions over the vertex McKissock et al also describe the serious prognosis in acute and subacute hæmatomas Here the complication of intracerebral hæmatoma is particularly important, and emergency angiography may prove an invaluable diagnostic measure

Dr Pygott and Dr Street (p 1371) return to the really important positive stage—namely, that of primary diagnostic screening If this stage breaks down or even is unduly delayed, three cases out of four exchange recovery for death or dementia

Coma invariably precedes death, but, where medullary herniation occurs, the onset of coma may coincide with respiratory arrest, and may precede cardiac arrest by only seconds or minutes

Important though it is to be reminded of the symptoms that may arise in this condition, it is even more important to realise the manifestations that may be absent Herein lies the real significance of these three contributions

ACUTE TUBULAR NECROSIS

THE views we lately expressed[1] have been supported by an analysis of 80 cases of acute tubular necrosis In this study Kiley et al[2] found that hæmodialysis by a Kolff rotating-drum artificial kidney was necessary in 60% of the cases, clinical rather than biochemical criteria being followed in deciding on this type of treatment Kiley et al consider that dialysis is more effective in preventing clinical deterioration than in improving the clinical situation after such deterioration has already occurred This finding necessitates earlier and more frequent use of the artificial kidney—usually at the first evidence of impaired cerebration from uræmia The series shows the usual difference in prognosis between the milder medical and obstetric cases and the more serious surgical group In the patients in whom renal damage was due to nephrotoxic drugs or poisons, transfusion reactions, or complications of pregnancy, the mortality was only 9%, whereas, of the cases secondary to surgical operations or accidental trauma, 65% died

The duration of the oliguric stage was thought to be of little importance in prognosis, but no case in this series had an oliguric stage lasting longer than twenty-four days The age of the patient is claimed to be much more important, 15% of patients under the age of 35, compared with 67% over 40, did not survive This difference may be due partly to the lower average age of the milder medical and obstetrical group If the cases due to accidental trauma and to surgical operations (excluding a particularly unfavourable elderly group where renal failure was secondary to aneurysmectomy) are considered alone, the fatality-rate was 64% above the age of 40 and 46% below that age—a difference which is not statistically significant The rate of protein catabolism, computed from the average daily rise of non-protein nitrogen, correlated well with the severity of the extrarenal disease and extent of tissue injury The figures varied from a rate of 30 g protein breakdown daily in the least severe cases to 150 g daily in the patients with serious injuries The abnormally high catabolic rate in the severe cases could not be controlled either by high carbohydrate intake or by administration of testosterone

Several other reports[3-5] show that results are now satisfactory in acute tubular necrosis from medical and obstetrical causes, but still unsatisfactory in surgical cases The first large surgical series was reported by a unit treating acute oliguric renal failure in battle casualties in the Korean war[6] This series is not, however, comparable to surgical cases in civilian practice Teschan et al[6] stated " The frequency and rapidity of potassium intoxication constitutes the most important difference between the post-traumatic renal insufficiency of combat casualties and the acute renal failure usually seen in civilian practice " They reported that plasma-potassium concentrations of more than 7 0 mEq per litre were found in a third of patients within the first four days after wounding This is rare in civilian cases, and it is unusual in most centres operating artificial kidneys to dialyse patients because of hyperkalæmia High serum-potassium in the military cases always resisted treatment with ion-exchange resins, whereas in civilian cases this therapy is usually effective Civilian injuries rarely involve large lacerations of voluntary muscle, which are common in injuries from modern high-velocity missiles The failure of therapy in the civilian surgical cases results from the deleterious effect of the uræmia on tissue repair, and the increased susceptibility to infection Salisbury[7] first suggested earlier and more frequent dialysis he recommended dialysis in all cases of acute tubular necrosis on the fifth day of the illness if clinical signs of uræmia were present, and on the sixth day if diuresis had not started Whilst this seems unnecessary in the medical and obstetrical cases, it is probably advisable in the surgical group Scribner et al[8 9] take an even more extreme view, which may well prove to be correct They have evolved two systems of therapy which they term " prophylactic hæmodialysis " and " continuous hæmodialysis " In the former, hæmodialysis is performed on alternate days in many cases, and in the latter, hæmodialysis has been applied continuously for as long as seventy-two hours Scribner et al claim that in the surgical cases treated before these systems were adopted the mortality was 71% of 41 cases—a figure comparable with those of other centres both in this country and the U S A Of 19 similar patients treated by their more heroic methods, only 37% died The two groups were shown to be comparable in age distribution and severity of injuries and uræmia

Until recently, centres operating artificial kidneys in this country have not been able to adopt such time-consuming methods, owing to the large number of patients referred for dialysis But most teaching centres are now equipped for this form of treatment, and with smaller numbers of patients involved there should soon be a gratifying improvement in the present unsatisfactory results in the surgical patients

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1 *Lancet*, Feb 13, 1960, p 371
2 Kiley, J E, Powers, S R, Jr, Beebe, R T *New Engl J Med* 1960, 262, 481
3 Bluemle, L W, Jr, Webster, J D, Jr, Elkinton, J R *Arch intern Med* 1959, 104, 180
4 Parsons, F M, McCracken, B H *Brit med J* 1959, i 740
5 Loughridge, L W, Milne, M D, Shackman, R, Wootton, I D P *Lancet*, Feb 13, 1960, p 351
6 Teschan, P E, Post, R S, Smith, L H, Jr, Abernathy, R S, Davis, J H, Gray, D M, Howard, J M, Johnson, K E, Klopp, E, Mundy, R L, O'Meara, M P, Rush, B F, Jr *Amer J Med* 1955, 18, 172
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9 Scribner, B H, Caner, J E 6

Special Articles

ASSUMPTIONS OF HEALTH SERVICE FINANCE

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LATELY GOODWIN TRAVELLING FELLOW OF ST JOHN'S COLLEGE, CAMBRIDGE, AT HARVARD GRADUATE SCHOOL OF BUSINESS ADMINISTRATION

IN this paper I examine the assumptions on which the financial structure of the National Health Service is based, and put forward an alternative method of financing it

INTENTIONS

The Beveridge report of 1942 made assumptions which were to have a profound effect on the service It proposed the introduction of " a national health service for prevention and for cure of disease and disability, by medical treatment ", which was to " be provided where needed " [1] The State was primarily interested " in finding a health service which would diminish disease "[2], and the cost of providing more elaborate and costly treatment would, it was thought, be offset by " a reduction in the number of cases requiring it " [3] Hence the annual cost of the service (£170 million) was not expected to rise in the twenty years between 1945 and 1965 It might even drop in later years, because the proposed medical service might " affect the possibility of diminishing and controlling sickness and so may affect the finances of the Social Insurance Fund " [4]

In June, 1942, the Medical Planning Commission, composed of members of the medical profession, considered the aims of a future medical service in this country to be " the achievement of positive health, the prevention of disease, and the relief of sickness ", made possible by making " available to every individual all necessary medical services " [5] It assumed that such a service could be financed " either by insurance methods or State funds " [6]

The objectives of the National Health Service Act of 1946 were the same as those proposed by Beveridge and the medical profession, and the means of achieving them were ensured by the financial provisions under section 52 " Any expenses incurred shall be defrayed out of moneys provided by Parliament." [7]

CHANGES IN PRACTICE

An estimate made at the end of 1947 for the first nine months of the health service, set the annual cost at £179 million. Early in 1949 a supplementary estimate of £53 million caused a heated discussion in Parliament One member, defending the service, opposed any suggestion for a limited fixed " sum of money which the Minister shall be permitted to expend " [8] Another asked rhetorically " What does it matter what the figure is if the needs of our people for medical, dental, and hospital treatment which they require call for such a figure ? " [9] This argument was countered by a speaker who did not agree " that the need of the people is the only criterion of the amount of money to be spent " [10], he pointed to the claims of other essential services on limited public funds Nevertheless, in 1955 the Acton Society Trust still thought it fundamental that the service should be " secured through the provision of national funds based solely on an assessment of needs, in accordance with the recommendation of the Beveridge report " [11]

At the end of 1948 the estimate of the cost to the Exchequer for 1949-50 was £228 million In early 1950 a supplementary estimate of £98 million outraged the Opposition, who deplored " the failure of the Chancellor of the Exchequer to enforce his own instructions to Departments not to overspend so extensively their Estimates " [12] The reply of the Chancellor, Sir Stafford Cripps, was unequivocal " I believe it is necessary to call a halt to further development of these services We must, therefore, regard the Estimates for the forthcoming year as a ceiling beyond which we must not be carried " [13] As part of the policy of applying a ceiling of £400 million on expenditure, the Labour Government in May, 1951, imposed charges for dentures and spectacles A few months later a Conservative Government came into office, and continued this policy " We shall keep the cost of this Service within a ceiling of £400 million," [14] said Mr Butler as Chancellor in January, 1952, but within two months the Danckwerts award made it impossible for the Government to maintain the ceiling, and in 1952-53 expenditure rose to £420 million *The Times* in February, 1953, remarked that though the principle of an upper limit to health service expenditure was no longer questioned, retention of the same figure became more difficult each year, and quoted Mr Macleod's words as a backbencher " We have been committed to a ceiling of £8 a head. There has been no examination to decide whether it should be £7, £8, £10, £11, we do not know I suggest that we should study the proportion which health ought to bear to the whole of our national expenditure " [15]†

Uneasiness about the cost of the health service persisted, both inside and outside Parliament. Finally, in April, 1953, the Guillebaud Committee was set up " to advise how, in view of the burdens on the Exchequer, a rising charge upon it can be avoided while providing for the maintenance of an adequate Service " [16] Reporting in 1956, it said that " the National Health Service has absorbed a decreasing proportion of the country's resources since the first full year of the Service ",[17] and after an exhaustive examination it " found no opportunity for making recommendations which would reduce in a substantial degree the annual cost of the Service " [18] But the country, even now, has still not recovered from the shock of the large supplementary estimates of the first two years of the Service, and the considerable miscalculations of the health service planners. Despite the Guillebaud report, a myth persists that the service is grossly extravagant

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† The national income is a measure of the money value of goods and services becoming available to a nation from economic activity over a period of time It can be regarded in three ways as a sum of incomes derived from economic activity (from employment and from profits), as a sum of expenditures (on consumption and on capital formation), or as a sum of the products of the various industries of the nation Thus, national income = national expenditure = national product

[1] Beveridge Committee Social Insurance and Allied Services, p 158 Cmd 6404 H.M Stationery Office, 1942
[2] *ibid* p 162
[3] *ibid* p 105
[4] *ibid* p 159
[5] Medical Planning Commission. *Brit med J* 1942, i, 743
[6] *ibid* p 746
[7] National Health Service Act 1946 9 & 10 Geo 6 Ch 81
[8] Messer F *Parliamentary Debates House of Commons* 1949 461, col 1377
[9] Fernyhough, E *ibid* col 1411
[10] Eccles, D *ibid* col 1430
[11] Acton Society Trust Hospitals and the State p 15 London, 1955
[12] Crookshank, H F *Parliamentary Debates House of Commons* 1950, 472, col 916
[13] Cripps, S *ibid* col 937
[14] Butler, R. A *ibid* 1952, 495, col 54
[15] Macleod I *ibid* 1952, 498 col 962
[16] Macleod, I *ibid* 1953, 513, col 1229
[17] Guillebaud Committee Cost of the National Health Service, p 10 Cmd. 9663 H.M Stationery Office, 1956
[18] *ibid* p 239

FIVE ASSUMPTIONS

These quotations suggest a change after the first year, in the objectives underlying the financing of the service Initially, public funds were to be supplied to provide medical care, with need as the sole criterion for the quantity of funds to be made available Within 18 months need was to be satisfied only within the arbitrary limit of £400 million per annum of public funds This was not a mere shift in emphasis it was a fundamental change of policy But both policies are based on false assumptions, and are difficult, if not impossible, to carry out

The assumptions underlying the service as planned include

1 *A publicly financed health service, by satisfying need for medical care as it arises, will result in a diminution or control of disease by prevention or cure*

This is false Improved medical care, whether privately or publicly financed, will prevent or cure individual diseases in individuals, but it does not control " disease " in any meaningful sense The pattern of disease in the community changes, " disease " does not diminish or disappear The child who, because of immunisation, does not die of diphtheria, smallpox or tetanus at the age of three, is cured of tuberculosis at the age of twenty, lives on to be treated for diabetes mellitus at sixty, becomes disabled by osteoarthritis at seventy, and dies at eighty from a cerebral thrombosis

2 *National expenditure on medical care can be determined by the need for medical care*

This assumption is not borne out in practice Observations in many countries suggest that national expenditure on medical care is primarily determined by national income[19, 20] It is quite evident that those nations most in need of medical care—if need be assessed by infant-mortality rate and the expectation of life—have a low per-capita expenditure on medical care, because they have a low per-capita income Those nations least in need of medical care have a high per-capita expenditure on it

3 *Since an improved health service will result in improved health and decrease the need for medical care, the cost of such a service after an initial rise will remain static or actually fall Thus expenditure on a health service can be self-limiting*

Both basic premises are false Control or prevention of individual diseases in individuals does not decrease the need for medical care in any absolute sense, and anyhow need does not determine the cost of a health service Expenditure on a health service is therefore not self-limiting, it is limited by national income and by demands on national income other than those of medical care

4 *The need for medical care—which often remains unsatisfied when its satisfaction depends on individual direct payments—can be wholly satisfied when payment is made collectively through public funds*

This could be true only if need was limited in some meaningful way, or if public funds were unlimited Neither of these propositions is true, and the assumption based on them is false

With these false assumptions as foundations on which the financial structure of the health service rested, a final assumption was made on which the financial tools of the service were fashioned

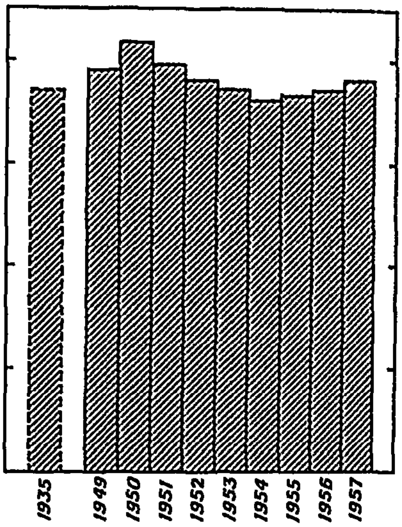

Fig 1—Expenditure on health services expressed as a percentage of gross national product, United Kingdom, 1949 57 and 1935

Sources 1949–1957, see table 1935, Political and Economic Planning, *Report on the British Health Services*, London, 1937, p 387

Expenditure on items of medical care in 1935 roughly comparable to the present health services was about £163 million

5 *Public funds can be provided for a health service using an assessment of medical needs as the sole criterion for expenditure*

This assumption, and all the previous ones, beg the question of what is need for medical care Does a patient need to be in hospital, or in a convalescent home, does he need a single room, does he need a blood-transfusion, does he need a carotid arteriogram, serum-electrolyte estimations, or an electroencephalogram, does he need an ambulance, does he need a laparotomy, does he need a consultant's opinion, does he need aneurine hydrochloride, delta-hydrocortisone, or tetracycline, does he need a home help, does he need a false tooth? To all these questions, and others like them, on which decisions must be taken daily, there are no answers valid for all people, in all places, at all times The concept of need for medical care is largely subjective, and it is relative The answers

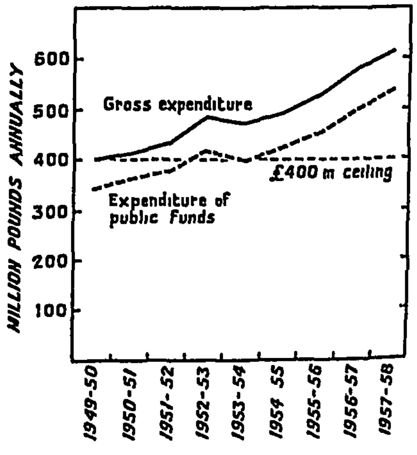

Fig 2—Expenditure of public funds and gross expenditure on the National Health Service for England and Wales during 1949 58

Source Ministry of Health annual report for 1958, part 1, table 1

Public funds as used here are those provided by the Exchequer and National Insurance Fund, local-authority funds derived from rates are excluded The abrupt rise in 1952–53 was due to the Danckwerts award, paid in this year, but including retrospective additions to general practitioners' incomes from 1948–51

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[19] Seale, J R *Lancet*, 1959 ii, 555

[20] International Labour Office Cost of Medical Care, p 152 Geneva, 1959

will depend on who is making the decision, when he is making the decision, and where he is making it

A criterion is a measure or standard Public funds are easily measured and limited in quantity To use a concept that is largely subjective and relative—and therefore immeasurable—as the sole criterion, or measure, for assessing the quantity of public funds to be made available is meaningless Some other criterion must be found

EFFECTS OF THESE ASSUMPTIONS

Expenditure on the National Health Service showed the initial rise predicted by the planners But the subsequent fall which they expected could not take place so long as the finance of the service was based on the criterion of need

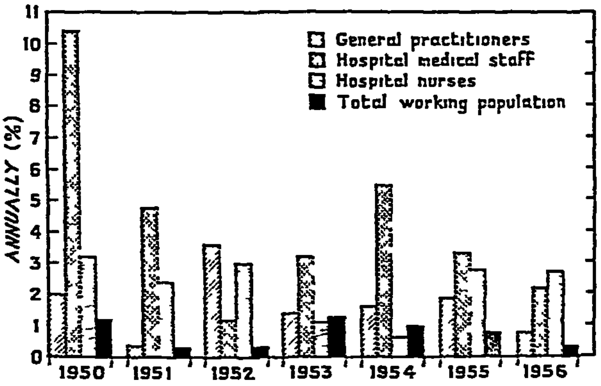

Fig 3—Annual percentage rise (over preceding year) of employees in National Health Service (England and Wales) and in the total working population.

Sources Ministry of Health annual reports, and Central Statistical Office, Monthly Digest of Statistics

General practitioners include assistants and trainee assistants Hospital medical staff expressed as whole-time equivalents Hospital nurses include part-time and student nurses

National expenditure on medical care in Britain rose rapidly between July, 1948, and 1950, not only in actual prices, but also as a proportion of national income. By 1950 the health services' expenditure accounted for 4·2% of gross national product (fig 1)

It is difficult to assess the proportion of national income spent on medical care in Britain before 1948, because the data are inadequate In the mid-1930s it was probably about 3·7%† of gross national product (fig 1) During the war it probably fell even further in Britain than in the U S.A. where the ratio was less than 3% in 1943, and where the pre-war ratio was not regained until 1949 Between 1947 and 1950 the ratio rose rapidly in Britain because of the changeover from a war-time to a peace-time economy, because some expenditure had been postponed in expectation of the introduction of the N H S, and because of the unusually high earnings during 1948–50 of some of those working for the service, particularly opticians and dentists All these factors were temporary, but even before they had ceased to be relevant the service was being financed on an entirely new assumption.

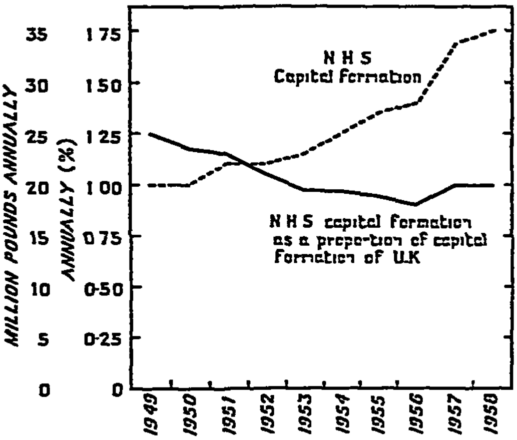

Fig 4—Gross fixed capital formation of the health services of United Kingdom, 1949–58

Source Central Statistical Office (1959) National Income and Expenditure, tables 47 and 53

Gross fixed capital formation is all expenditure on buildings, machinery, vehicles, or plant which will give service for more than a year

When the increasing drain on public funds alarmed politicians and taxpayers, a limit was placed on the quantity of funds provided The fifth assumption was in practice replaced by a new one

6 *National expenditure on medical care in a modern industrial State can be limited to a constant cash figure over many years by political decision, without adversely affecting the quality of the care provided*

This assumption would be reasonable if the first four

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† This proportion is only a rough indication of pre-war expenditure, it is certainly not directly comparable to the other proportions given in fig 1, which are themselves internally consistent

GROSS EXPENDITURE OF PUBLIC HEALTH SERVICES—UNITED KINGDOM 1949-1957 (MILLION POUNDS)

Year	Central government		Local authorities			6	7	8	9
	1 Current expenditure on goods and services	2 Gross fixed capital formation	3 Current expenditure on goods and services	4 Gross fixed capital formation	5 School health service	Expenditure by patients on N.H.S charges	Gross expenditure on health services	Gross national product	Ratio of health services' expenditure to gross national product
1949	369	12	44	3	6	3	437	11,129	3·90
1950	414	13	44	3	7	3	484	11 657	4·15
1951	427	14	49	3	7	8	508	12,839	3·95
1952	436	13	53	3	8	20	533	13 957	3·80
1953	450	14	55	3	8	24	554	14 922	3·70
1954	464	16	57	3	9	25	574	15 945	3·60
1955	499	18	62	3	10	26	618	16 992	3·65
1956	549	18	68	3	11	28	677	18,267	3·70
1957	591	24	73	3	12	32	735	19,370	3·80

Sources

Column 1 Central Statistical Office (1959) National Income & Expenditure, table 35
" 2 *ibid.* table 36
" 3 *ibid* table 38
" 4 *ibid.* table 39
" 5 Central Statistical Office, Monthly Digest of Statistics May, 1959, table D
" 6 *ibid* table B
(In the Monthly Digest expenditure is given by the financial year I has been assumed here that this was the same as in the earlier calendar year)
" 8 Central Statistical Office (1959) National Income & Expenditure, table 1
See also Central Statistical Office (1956) National Income Statistics Sources and Methods p.

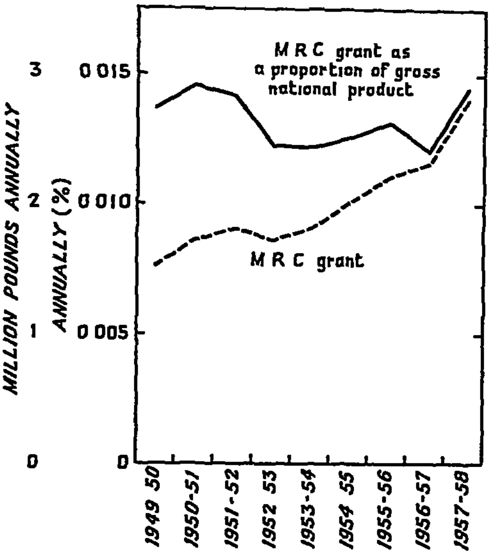

Fig 5—Medical Research Council grant from the Central Government, 1949–58

Source Central Statistical Office, Monthly Digest of Statistics, May, 1959, table B

It has been assumed that gross national product was the same in the financial year as in the calendar year

were true but they were not (Many people still regard them as sound and attribute their failure to be realised to some defect in the working of the service or in medical practice Such people talk of "our National Ill-health Service", or the necessity for "positive health and a preventive approach to medicine", or the "paradox" of health-service costs rising while indices of national health improve) It would be reasonable if the proportion of the working population providing medical care decreased with medical advance and industrial development but it does not—indeed the reverse is true It would be reasonable if national income remained static, but if national income rises, whether because of inflation, increased productivity, or an increased working population, then the greater the rise, the greater the unreasonableness of the assumption

The gross national product in the United Kingdom rose from £11,687 million in 1950 to £19,370 million in 1957—a rise of 67% If total expenditure by the National Health Service was £400 million in 1950 and had remained the same in 1957, the percentage of the gross national product spent on medical care would have fallen by some 40%—from 3 45% to 2 05% Such a fall in peace-time would be contrary to the experience of other nations throughout the world

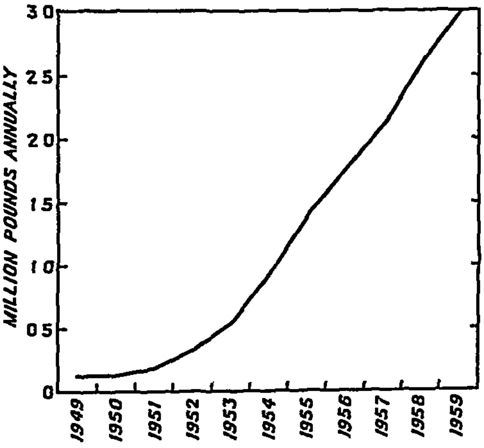

Fig 6—Gross annual income of British United Provident Association, 1949–59 (year ending June)

Data given in an article in the *Financial Times* (Dec 8, 1958) suggest that over three-quarters of private medical care insurance in Great Britain is handled by B U P A

EFFECTS OF THE SIXTH ASSUMPTION

If, in a health service which is State-operated and financed, and practically a monopoly supplier of medical care, expenditure is limited for some years to a constant figure while national income rises by two-thirds, one would expect the following consequences

A The attempt would fail Such intolerable strains would be produced within the service that it would be considered politically more desirable to let expenditure rise than to keep within the limit

Fig 2 shows that expenditure of public funds on the National Health Service in England and Wales, and the gross cost, has in point of fact risen annually since 1950 (after the abnormal effects of the Danckwerts award in 1952-53 have been discounted)

B The proportion of national income devoted to medical care would fall The more it fell, the greater the difficulty in making it fall further, and the lower the level reached, the greater the difficulty in maintaining it In due course the proportion would be expected to rise again

The table shows expenditure on the health services in the United Kingdom, and the gross national product, since 1949 Fig 1 shows the former expressed as a percentage of the latter After a rapid fall from 1950 to 1954, this percentage has risen slowly

C In so far as the attempt was successful, the number of people employed by the service would fall, relative to the rest of the working population, or their incomes would fall, relative to the incomes of the rest of the working population, or capital expenditure would fall, relative to the rest of the economy

The number of NHS employees, relative to the rest of the working population, seems to be rising rather than falling (fig 3) Since 1949 the average incomes of some categories of employees have fallen, relative to the average incomes of other workers From 1949 to 1956 capital expenditure on the health services, as a percentage of all capital expenditure by the nation, fell steadily (fig 4)

D *Medical research would be starved of funds*

The share of the national income received by the Medical Research Council fell substantially between 1950 and 1956 (fig 5)

E The flow of funds from private sources outside the State service would increase

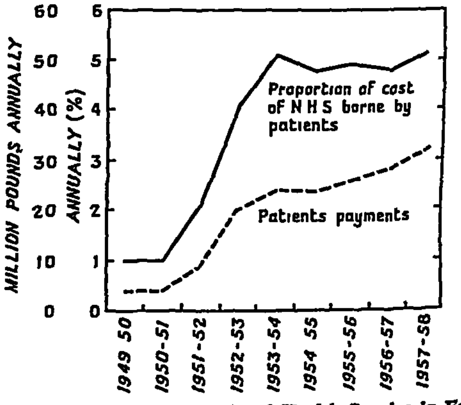

Fig 7—Patients' payments to National Health Service in England and Wales during 1949–58

Source Ministry of Health annual report for 1958, Part 1, table I

Health insurance provided by the British United Provident Association is on a relatively small scale, but the Association's gross income increased twenty-three times between 1950 and 1959 (fig 6)

F The proportion of the cost of the health service borne by direct patient payments would increase

Fig 7 shows that the proportion of the cost of the service borne by direct payments by patients rose from 1% in 1949 to 5% in 1953 and has since remained at that level

ASSUMPTIONS FOR THE FUTURE

Many of the basic financial assumptions of the National Health Service as planned, and as operated so far, are pragmatically unsound they do not work For the future more realistic assumptions are needed

I suggest that the objectives should be

The best medical care that the nation can afford—not the cheapest it can get

A service primarily financed by taxation or by insurance

If I am right in my observation [19] that, in the absence of major wars or economic depressions, the proportion of national income devoted to medical care tends to remain constant over many years, whether it is publicly or privately financed, a method of financing a health service could be evolved as follows

Determine by political decision the range of services to be provided free of direct charge

Determine the percentage of national income these services had absorbed over the preceding ten to twenty years

Determine by political decision the public funds to be provided for the health service for the next five years or so, as a percentage of national income

This percentage would be a " ceiling " beyond which public funds would not rise, a " floor " below which they would not fall, and it would recognise the fact that the " building " itself has a tendency to expand Need for medical care could then be satisfied within these limits, on a priority basis, as effectively as human fallibility would allow

A health service based on these assumptions would be financed and administered differently from our present one But the National Health Service, after all, is nothing more than an organisation for financing and administering medical care It is not the medical care itself, though the quality of the medical care can be adversely or favourably affected by the financial and administrative system New assumptions imply, therefore, a new health service, and maybe a better one

SUPPLEMENT TO ROYAL COMMISSION'S REPORT

The Royal Commission on Doctors' and Dentists' Remuneration, which reported four months ago,[1] in its inquiries sent a postal questionary to doctors, dentists, and members of other professions A further statistical appendix, now published,[2] sets out data from this survey which the Royal Commission considered to be less directly connected with its task but still of great interest in a study of remuneration and conditions of service in the major professions

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[1] Royal Commission on Doctors and Dentists Remuneration 1957–60 Cmnd 939 H.M Stationery Office, 1960 See *Lancet*, Feb 20, 1960, pp 421, 427

[2] Royal Commission on Doctors and Dentists Remuneration 1957–60 Supplement to report further statistical app [illegible] M Stationery Office, 1960 Pp 42 2s 6d.

Points of View

FROM BOTH ENDS OF THE TABLE

(or The Art of Surgeon Management and Anæsthetist Toleration)

K F Hulbert
M B Lond, F R C S, D A.
CONSULTANT ORTHOPÆDIC SURGEON, DARTFORD GROUP OF HOSPITALS

The partnership between surgeon and anæsthetist is unusual and important There has been a great change in this relationship of recent years, from that of the surgeon and his lackey to that of the anæsthetist depicted in a cartoon as boasting on the doorstep of a hospital as to the number of surgeons he has working for him Neither of these two extremes represents the true surgeon-anæsthetist relationship, and as in so many other human relationships the middle way represents what is best for all

The art of understanding people was described by Ezekiel in the words " I sat where they sat " Having been an anæsthetist first and then a surgeon later, and having seen the foibles of the surgeons from the anæsthetist's stool, and the idiosyncrasies of the anæsthetists from the surgeon's end of the table, the development of this partnership may be helped by relating some experiences and reactions of both the anæsthetist and the surgeon

THE ANÆSTHETIST'S VIEW

First, then, the anæsthetist's view of the surgeon This view has varied in the past from that of a cringing slave or fawning sycophant to that of a condescending and rather superior technician The anæsthetist has always been regarded as a junior partner and has tended to look up to the surgeon, and this has perhaps made him at times jealous of his own preserves, tending to resent any intrusion into those regions that he has rightly looked on as his own

The place that the anæsthetist rightly claims as his own is the anæsthetic room The anæsthetic room is the anæsthetist's very, very own, and the surgeon must not intrude therein The surgeon should realise that delay in the anæsthetic room is due to troubles that only the anæsthetist can manage and overcome The anæsthetist is not spending a long time in the anæsthetic room just to annoy the surgeon and any attempt by the surgeon to hurry him up by peering through the door, or even shouting through the key-hole, only arouses those natural obstinacies which the anæsthetist, being human, is heir to, and, far from being quicker under these circumstances, he may even take longer than ever The surgeon should always remember that the anæsthetist is king in the ante-room even if he has to surrender his sovereignty on wheeling his patient into the royal presence next door Finally it should be pointed out to surgeons that to burst into the anæsthetic room and talk in a loud voice or to handle the patient as he is being gently and carefully launched on to the waters of Lethe by the priest of the cult, is just plain bad manners It is also rather a thoughtless interference with the anæsthetist's most precious possession—his short and tenuous hold on the doctor-patient relationship The surgeon enters fully and freely into this most precious facet of Medicine. I used to feel acutely in my anæsthetic days the loss of personal relationship between the doctor and his patient, and only the brief interlude in the anæsthetic room takes the place of the relationship which my colleagues used to enjoy The fact that so many anæsthetists are seeking closer relationships with their patients by visiting them both before and after the operation in the wards is one of the most pleasing developments in the art of anæsthetics The anæsthetist is often presented in the anæsthetic room with a frightened stranger whom he has to help through the most important crisis in his life, and it is his privilege to employ his art and skill to make this experience, from the patient's point of view, a brief and pleasant personal relationship The anæsthetic room was devised as a means to spare the patient the ordeal of waiting in the operating-theatre, but the complexity of modern anæsthetics, with the multiplicity of syringes to be filled and apparatus to be adjusted, is such that an ante-room to the anæsthetic room is sometimes needed The anæsthetic room should be like the room depicted by John Bunyan " The pilgrims they laid in a large upper chamber, whose window opened towards the sun rising, the name of the chamber was Peace "

Partnership is news The idea of partnership between races, partnership in industry, partnership between individuals, is commonplace in this modern world, and yet the importance of being able to get on with other people underlies the whole story of mankind The Book of *Proverbs* says " He that walketh with wise men shall be wise, but a companion of fools shall be destroyed ", and there is wisdom in the advice that a partnership between two people should be the right kind of partnership in order to succeed

Once the doors of the anæsthetic room are opened, the anæsthetist's brief reign is almost over He is, however, still responsible for the patient until the surgeon begins the operation, and nothing pleases the anæsthetist more than to be asked by the surgeon for permission to begin —unless it is the few words of thanks at the end of the operation. Once the operation has commenced, of course, the aim of the anæsthetist in his relationship with the surgeon is to make himself obscure and almost unobserved In order to do this he must be left to mind his own business, which is the administration of the anæsthetic The surgical dilettante who " gave anæsthetics as a houseman " and who interferes with the anæsthetist is just a menace A joint consultation beforehand is desirable and even essential, but a quarrel in the theatre is a disaster

THE SURGEON'S VIEW

Now for the surgeon's view of the anæsthetist Operative surgery is a very exacting occupation, and it can be a very nerve-racking affair for the surgeon From my anæsthetist's stool at the head of the table I often used to wonder why it was that when the surgeon got into difficulty during an operation, he used to pour with sweat whilst all his assistants remained cool and dry Now I know It has to be experienced to be believed The nervous strain of long operating-lists can be very great, and nothing makes things worse than to have to pound up and down the theatre floor, gowned and gloved, waiting for the patient to come in This is especially aggravating when a list of short cases is presented, because the rhythm of going from one to the other evenly and smoothly is much less tiring when there are no frustrating delays in between each case

The old anæsthetists of the rag-and-bottle era, whilst having their Herculean struggles in the anæsthetic room, did pride themselves on their ability to get the next patient on the table as the former one was being lifted off The modern anæsthetist of the " kick him, he is still breathing " era, whilst producing for us beautifully quiet and relaxed anæsthesia of almost unbelievable safety, does seem to take an unconscionable long time about it in the anæsthetic room, and, by Jove, it can be frustrating!

Again, from my anæsthetist's stool I used to wonder why surgeons were often taciturn in the theatre Now I know It is because the concentration required of surgeons is beyond the comprehension of those who have not experienced the strain of long and complicated operations To have the train of thought broken by idle chatter whilst following the steps of a complex operative procedure is nearly grounds for justifiable homicide I can remember on one occasion, when I was approaching the climax of a very long and technically very difficult operation, the anæsthetist said in a loud voice from the other end of the table " How on earth is the patient ever going to walk again?" I had a heavy orthopædic hammer in my hand at the time, and it was only the fear of the great deterrent that prevented the hammer being applied to something other than the head of the osteotome The good anæsthetist knows when to talk and when to be silent He should talk when the surgeon wants to relax, and he must keep quiet when the surgeon wants to concentrate He should never ask the surgeon what he is trying to do when the surgeon is obviously oblivious to everything except the nerve-root or the venous plexus that he durst not tear The anæsthetist should try to understand that when the surgeon talks aloud and asks his advice during a difficult operation as to what he should do, he is only expecting the anæsthetist to agree with him and give him his support, not to argue about things beyond his ken

The ideal anæsthetist in the eyes of an anæsthetist is probably an expert technician, but in the eyes of the surgeon he is much more He is a doctor, possessed of almost feminine intuition as to the surgeon's feelings, and with an ability to sum up the patient's condition and render a physiological balance-sheet at any stage of the operation This ability is beyond that of the mere technician, and the surgeon still recognises a man with a " flair for anæsthetics "

It might well be asked how such divergent characters as surgeons and anæsthetists could possibly get on with each other and cooperate in the welfare of the patient Yet the medical profession is full of such partnerships, often of widely differing personalities, yet both combining in the interests of the patient to work together for his and their own good

The secret of success in this partnership is mutual understanding, each the result of close prior consultation with the other and of longstanding cooperation in many situations The anæsthetist should learn the ways of his surgical colleague and should know enough of what is going on at the other end of the table to help in an unobtrusive way both by his skill and understanding as the various steps of the operation proceed The patient who kicks at the first application of the surgeon's scalpel to his foot can be as dangerous as the anæsthetist who talks at the wrong moment or who fails to talk at the right moment The surgeon never likes to be left alone in the theatre, and the prophets who foresee anæsthesia by automation and remote control have never known the feeling of confidence engendered in the theatre by a good anæsthetist.

Then again, the anæsthetist should always remember that the patient is primarily the surgeon's patient He it is who saw the patient in the outpatient department and perhaps persuaded him and his anxious relatives that he should undergo the operation He it is who has promised him that all will be well, that he will feel no pain, and that Dr A is a good anæsthetist in whom he has every confidence He it is who must see the patient and relations if anything goes wrong The surgeon carries the burden of his patients before, during, and after the operation The surgeon has come to know his patient as a person of individual worth and infinite value to his family circle

The anæsthetist shares in this by being what all good anæsthetists should be—a good doctor The visit to the patient beforehand, and advice to the surgeon on fitness for operating, halves the immediate burden of decision The mere technician or experimental physiologist whose idea of the doctor-patient relationship is a curt "hold out your arm" in the anæsthetic room increases this burden no matter how skilful he may be in his anæsthetic technique Then again, the anæsthetist, wise and experienced in resuscitation and the management of theatre routine, greatly reduces the load of anxiety in the operating-theatre The occasional minor crises, from a nurse fainting to a compressed-air cylinder not working, can all be overcome by the watchful anæsthetist whilst the surgeon pursues his way unmolested Then, when the tension is over, or whilst awaiting an X-ray film, the good conversationalist is a most pleasant person to have as a barb to one's wit or just as "someone to talk to"

Finally there is that most pleasant of all occasions—tea in the surgeon's room (*4d* per head these days)—presided over by the anæsthetist whilst his tired colleague relaxes in the chair What utter bliss!

PARTNERSHIP

The rise of the anæsthetic specialist from the chloroformist of old to his present position of equality is one of the most striking events in modern medicine The most recent developments in surgery and anæsthesia have produced a far closer relationship than ever before between surgeon and anæsthetist, and there is no doubt that the position of the anæsthetist is well established and secure There are still those who grudge him his new-found eminence and his economic parity Is he really worth it? Well, let him be skilled in his trade, be kind and considerate both to his patients and to his colleagues, be unobtrusive when not wanted and plainly evident when he is needed Let him be guide, philosopher, and friend to all in the theatre, reliable and helpful in the welfare of the patient in all phases of his surgical treatment, and in short let him be a good doctor—then he is worth his weight in gold, and that in some instances is a considerable amount

As Paul said of the runaway slave Onesimus "that thou shouldest receive him for ever, not now as a servant, but above a servant, a brother beloved"

Medicine and the Law

Deterioration and Institutional Environment

THE parties were married in 1942 From 1946 the wife showed signs of mental instability She evinced a pathological dread of contamination The matrimonial home had to be changed several times because of the wife's attitude to her environment and her fear of contact In 1947, after the birth of a child, her condition improved for a time and then deteriorated She threatened to commit suicide more than once In March, 1951, she attempted to gas herself She survived but killed her child In May, 1951, she was tried for murder and found guilty but insane On June 1, 1951, she was admitted to Broadmoor where she had been detained as a patient ever since

In October, 1959, the husband sought dissolution of the marriage on the ground that the wife was incurably of unsound mind The official solicitor, as guardian ad litem of the wife, denied that she was incurably of unsound mind

At the hearing, Dr P G McGrath, physician-superintendent at Broadmoor, said that the wife had severe, chronic, obsessive, compulsive psychoneurosis A prefrontal leucotomy in 1950 had alleviated her distress, but severe intracranial hæmorrhage had supervened, resulting in severe epilepsy, and personality changes had taken place evidenced by a pathological preoccupation with her bodily functions and gross deterioration in her habits She had been under his care since 1956 and, despite every known form of treatment, was showing slow but steady deterioration She was incapable of living independently outside hospital Without professional aid and supervision she would find the complexity of life intolerable and might well again become depressed to the point of suicide She was incurably of unsound mind Dr J L F Maine, the senior registrar at Broadmoor, confirmed Dr McGrath's evidence

Dr Joshua Bierer, who had examined the wife once in February, 1960, accepted the diagnosis of Dr McGrath and Dr Maine, but could not accept their evidence as to deterioration since he held that such a degree of deterioration must entail a deterioration in rationality and he could find none He said that the right treatment necessitated her release from hospital she had paid her debt to society and would have a much better chance of recovery if she lived outside an institution Although he had reported that the wife had never been, and never was, likely to be a danger to anybody he was not prepared to advance the opinion that if the wife were released from an institution all her symptoms would disappear, but that there was a good chance of her improving to a point at which she would be able to manage her own life and affairs He also said that the prolonged opportunity of Dr McGrath and Dr Maine for observing the wife's obsessions, so far from adding to the value of their opinions, might well be a disadvantage, in that doctors who work in institutions could not help seeing things from a definite angle and their outlook was unconsciously coloured by their environment

Mr Justice COLLINGWOOD said that Dr Bierer's theory that the wife's present condition only needed freedom from institutional life to alleviate it seemed hardly consistent with the history of the case Before her reception as a Broadmoor patient there was a long history of mental disorder, necessitating electric shock treatment on two occasions followed by leucotomy and culminating in the killing of the child In those circumstances it was difficult to conceive that the institutional environment had had a detrimental effect on her Dr McGrath entirely rejected that theory and doubted whether institutional neurosis existed at Broadmoor In his opinion the treatment she had received had done a great deal in that it had retarded her deterioration Having regard to the circumstances leading to the wife's becoming a Broadmoor patient, it was difficult to understand the opinion expressed in Dr Bierer's report that she had never been a danger to anybody and his prognosis must be considered in the li[illegible] t opinion

His Lordship could find no good reason in the evidence before him for rejecting the view of Dr McGrath that the wife was incurably of unsound mind since she was not in, nor could she hope to be restored to, a state in which she would be capable of managing herself or her affairs The husband was, therefore, entitled to a decree in the exercise of the court's discretion

De Wolf *v* De Wolf—*Probate Divorce and Admiralty Division* Collingwood, J, June 2, 1960 John Mortimer (Bernard W Main), R B Holroyd Pearce (the Official Solicitor)

ELAINE JONES
Barrister-at-Law

Congresses

CLINICAL PATHOLOGY

THE fourth International Congress of Clinical Pathology was held in Madrid on June 13–17 More than four hundred pathologists from 36 different countries were present A few of the contributions are summarised here

Immunohæmatology

Dr J MOULINIER (Bordeaux) discussed the antigenic structure of platelets and its possible role in the ætiology of disease It had been shown that platelets shared ABO, Rh, Kell, and Duffy antigens with erythrocytes—which accounted for the rare purpuric syndrome that sometimes complicated hæmolytic disease of the newborn By applying differential agglutination techniques it would be possible to study the survival of transfused platelets Platelets also possessed their own specific antigens by which they could be classified into two main antigenic groups—" Duzo " and " Ziv " These specific antigens could be responsible for anti-platelet immunisation after transfusion nullifying the effect of transfusion of concentrated platelet suspensions, and making it necessary to cross-match donor platelets with recipient's serum before transfusion, fœto-maternal platelet incompatibility could also occur, giving rise to neonatal immunological purpura In more than 70% of cases of idiopathic thrombocytopenic purpura it could be shown that the platelets were coated with globulin, which Dr Moulinier considered was auto-antibody globulin and which was responsible for the thrombocytopenia Demonstration of the presence of this globulin on the platelets in patients with idiopathic thrombocytopenic purpura was an indication for splenectomy provided that purpura secondary to lupus erythematosus had been confidently excluded

Mycobacterium Lepræ

Prof C E LUMSDEN (Leeds) reviewed various methods for culturing *Mycobacterium lepræ* and gave an account of his experiments in cultivating the organism in animal and human tissue cultures He found that it could be propagated only with difficulty and with notably inconsistent results in all the human and animal tissues used except cultures of Schwann cells, which selectively took up the organism, which then multiplied intracellularly for a short time The bacilli remained morphologically unaltered in the Schwann cells for some 39 days, in contrast to their rapid degeneration extracellularly or intracellularly in other tissue cultures Only a small fraction of the bacilli in a patient's skin might be viable at the time of biopsy

Staphylococcal Enzymes

Dr MARY BARBER (London) gave an account of the enzymes of the staphylococcus, study of which might be helpful in differentiating pathogenic from non-pathogenic strains of the organism Of these the most useful from the point of view of laboratory differentiation was coagulase Free coagulase, to which she confined her remarks, was antigenic, and that from different staphylococci of human origin could be divided into three antigenic types corresponding to the three main phage groups Most normal people had antibodies to one or more types of coagulase There was no correlation between enzyme production by a strain and its virulence Penicillinase production by staphylococci was greatly increased by the presence of penicillin, but penicillinase production could not be evoked by growing penicillin-sensitive staphylococci in the presence of penicillin Penicillinase-producing strains of staphylococci continued to produce the enzyme after passage for long periods in the absence of penicillin, although many strains tended to yield a proportion of cells which had completely lost this capacity

Tumour Enzymes

Dr G VAN RIJSSEL and Dr R J G WILLIGHAGEN (Leyden) had examined the enzyme content of 300 human tumours They found that several tumours had a characteristic enzyme pattern, which was reproduced in their metastases These workers had identified tumours of unknown origin by determining their enzyme pattern. The pattern seemed to vary according to the degree of differentiation of the tumour tissue, which might indicate the degree of malignancy and the clinical prognosis

Uptake of Triiodothyronine by Red Cells

Dr C T C CHOW and Dr O B HUNTER (Washington, U S A) presented the results of their studies of the uptake of *l*-triiodothyronine tagged with ^{131}I by the red cells of 100 normal newborn infants They found that the uptake was 20–30% with no significant sex difference The test was performed in vitro on only 3 ml blood, thus eliminating any radiation risk to the patients and the necessity for large quantities of blood Other workers had shown that radio-triiodothyronine uptake by red cells was a valuable indication of thyroid function in adults, and this might provide a useful, comparatively simple screening-test for hypothyroidism at birth, especially in endemic areas

V.M.A Excretion

Dr M SANDLER and Dr C R J RUTHVEN (London) described their experience in measuring the urinary excretion of 3-methoxy-4-hydroxymandelic acid (V M.A) in patients suspected of having a phæochromocytoma V M A had been identified as a major metabolite of adrenaline and noradrenaline Its excretion was increased in every patient with histologically confirmed phæochromocytoma whom they had investigated One patient, suspected clinically of having a phæochromocytoma, who had a normal urinary catecholamine excretion, had a raised V M A output and was found at laparotomy to have such a tumour Patients with essential hypertension and raised urinary catecholamine excretion had normal V M A excretion Some patients with carcinoid tumours had been shown to have raised V M.A excretion

Plasma-insulin

Dr J L R CANDELA (Madrid) reviewed the usefulness of estimations of insulin in plasma From the clinical point of view the estimation permitted the certain diagnosis of hyperinsulinæmic hypoglycæmia due to insulin-secreting adenomas of the islet cells of the pancreas Furthermore, useful information could be obtained concerning the ætiology of abortions, fœtal malformations, and macrosomia associated with abnormalities of insulin metabolism Application of this technique to physiological preparations would help to clarify the site in the muscle cell at which insulin exerted its action It was likely, and very interesting, that muscular and adipose tissue responded in different ways to different fractions of circulating insulin, especially to insulin combined with plasma-proteins A great deal of work remained to be done to solve the many problems posed by the insulin-effect of plasma The preparation of the patient on whom the test was to be done was important Thus blood for the estimation should be drawn with the patient fasting and after a good night's rest, and without any emotional disturbance If a normal result was obtained in a patient strongly suspected of having an insulin-secreting adenoma, the test should be repeated by collecting blood 5–15 minutes after an intravenous injection of 20 ml of hypertonic glucose solution It was most important in such cases to collect the blood during the period of hyperglycæmia

Heparinised plasma was used for the test He employed the rat-diaphragm technique, and he emphasised the importance of the preparation of the rats

Urinary Œstrogen

Dr C **Hensghem** and Dr G **Cession** (Liège) reviewed the results of urinary œstrogen determinations They commended the Brown and Beruld method of estimation but pointed out that it was considered by many workers to be too elaborate for routine use, for which the methods of Jayle were more suitable even if less precise. For the purpose of clinical diagnosis there were three possibilities first, to determine the urinary excretion of endogenous œstrogen, second, to determine the urinary œstrogen excretion after stimulation of the ovary or testis by giving gonadotrophic hormones, and third, to study the urinary œstrogen excretion after administration of œstrone or S-œstradiol. Urinary excretion of endogenous œstrogens gave information about changes in ovarian activity during the menstrual cycle and pregnancy, and reflected abnormalities in ovarian function which could be of diagnostic, therapeutic, and prognostic significance. The effect on urinary œstrogen excretion of stimulation of the ovaries by gonadotrophin gave interesting information in patients with sterility, primary amenorrhœa, or repeated abortions In men, study of urinary œstrogen excretion after stimulation of the testis with gonadotrophin was helpful in elucidating the ætiology of sexual immaturity, eunuchoidism, and the Klinefelter syndrome, but such tests could be dangerous Finally the adrenocortical contribution to œstrogen excretion could be assessed by giving radioactively labelled œstrogen and determining the proportion of tagged to normal œstrogen excreted in the urine This technique had demonstrated differences in œstrogen metabolism between the newborn and the adult.

Diagnosis of Hepatic Disease

Dr F **Wuhrmann** and Dr B **Jasinski** (Zurich) reviewed the metabolism of iron-protein complexes and various enzymes in hepatic disease. The iron-protein complex could be differentiated into "function proteins", depot proteins, and transport proteins Of these the last two were particularly affected in liver disease. Damage to the liver cells caused loss of hepatic intracellular iron, because the cell's capacity for retaining iron was impaired Serum-iron levels increased, and other intracellular substances, such as enzymes and vitamin B_{12}, left the liver cells and appeared in the blood Cæruloplasmin, which was one of the α_2-globulins, was decreased, and this was generally accompanied by low serum-copper levels in hepatolenticular degeneration Serum-enzyme concentrations rose in liver disease before any alteration could be detected in serum proteins or bilirubin Such increases of enzymes were an indication of activity of the disease process, and serial estimations in the course of the disease were valuable prognostically In infective hepatitis the heterogeneous γ-globulins of the serum increased while serum-albumin fell Serum iron-binding capacity was often completely saturated, and the serum-iron was increased in 90% of cases Increased enzyme activity was usually accompanied by a rise in serum-vitamin-B_{12}. In contrast, in obstructive jaundice especially in the early stages, there was little or no alteration in serum-protein levels, serum-iron was low, and serum-alkaline-phosphatase alone of the enzymes was increased There were only minor fluctuations in serum-γ-globulins in fatty degeneration of the liver In alcoholic cirrhosis there was often a precedent fatty change, and in some cases serum-transaminase and aldolase were increased In late stages of the disease serum-albumin fell and γ-globulins increased In biliary cirrhosis unexplained hyperproteinæmia could occur, and there was much increase of α_2-globulins In the congested liver of cardiac failure, where increased γ-globulinæmia was often associated with a normal erythrocyte-sedimentation rate, the alterations in serum-proteins were often reversible For differential diagnosis of liver disease these workers recommended estimations of serum-iron and of serum-alkaline-phosphatase, but they [illegible] the great importance of careful history-taking and [illegible]nation to which laboratory tests could only be occasionally useful adjuncts

Prof N F **Maclagan** (London) read a paper on the efficiency of some popular tests in the diagnosis of hepatic disease Quantitative estimations of bilirubin and urobilinogen were of most value in differentiating prehepatic jaundice from other varieties Confirmation of a diagnosis of prehepatic jaundice depended on hæmatological tests and red-cell-survival estimations using erythrocytes tagged with radioactive chromium The most difficult task was to distinguish hepatic from posthepatic jaundice and to this end a multitude of flocculation tests and enzyme determinations had been devised Statistical analysis of the value of individual tests, or of certain tests in combination, was too complicated for routine application, and he had evolved a "diagnostic efficiency index" (D.E.I.) by which to assess the usefulness of certain tests in common use. The D.E.I. was calculated as the means of the percentages of results of any test alone or in combination with another, which gave correct positive and negative results in hepatic and posthepatic jaundice It represented the percentage probability of correct diagnosis in a case randomly chosen from a mixed group consisting of equal numbers of hepatic and posthepatic cases A test whose D.E.I. was 50% or less was diagnostically useless, while one with a D.E.I. of 100% would be the perfect test, though such a one had not yet been devised He listed 6 single tests with D.E.I.s of 75–87% of which cephalin-cholesterol flocculation, thymol flocculation, and serum-alkaline-phosphatase estimation had D.E.I.s of 80% 85%, and 87% respectively, the D.E.I. of thymol flocculation and serum-alkaline-phosphatase together was 90% Of the commonly used tests these two were the most valuable Recently two new tests had been described which showed considerable promise These were, first the estimation of the ratio of trihydroxy- to dihydroxy-bile acids in the serum, which was technically rather difficult, and secondly the Jirgl flocculation test which depended on alterations in the serum-mucoprotein fractions and which had a D.E.I. of 96% Of other tests of liver function he had found electrophoresis of the serum-proteins helpful in distinguishing the hypergammaglobulinæmia of hepatitis from hyper-α-globulinæmia of posthepatic jaundice The prothrombin-time should always be estimated if there was a possibility of surgery, the response of the prothrombin test to loading with vitamin K was helpful only if the prothrombin-time was abnormal initially Estimation of the serum-glutamic-oxaloacetic transaminase had a D.E.I. of 78% but was only helpful in the diagnosis of infective hepatitis in the first week at most of the disease There were a number of anomalous hepatitic diseases such as cholestatic jaundice, the Crigler-Najjar and Gilbert syndromes, and the Dubin-Johnson syndrome, in which the routinely used diagnostic laboratory tests were not very helpful Professor Maclagan concluded by stressing the vital importance of history-taking and clinical examination in the diagnosis of hepatic disease

Public Health

Live Poliomyelitis Vaccine in England

Bedfordshire County Council's health committee has agreed to participate in a limited trial of oral poliomyelitis vaccine of the type developed by Dr A B Sabin of Cincinnati, U S.A

The committee was informed that the Ministry of Health had approached about twenty local health authorities including Bedfordshire, seeking their cooperation in a small clinical study of vaccination by an oral method, with the objects of ascertaining the optimum dosage and of gaining experience of such vaccination in this country The studies are being carried out by the Medical Research Council in cooperation with the local health authorities In each area about 25 children aged 6–9 months will with the consent of the parents after full explanation, be vaccinated in this way

Dr W C. V Brothwood county medical officer of health, emphasised that the trial would not in any way affect the current programme of immunisation with killed vaccine

In England Now

A Running Commentary by Peripatetic Correspondents

I WAS leaning on a gate set in the narrow lane up the side of a hill, and thinking about nothing in particular ('gaffering' is the local word) except that the last week in May must surely be the most beautiful time of the year to take a holiday There was no sound or sight of humanity until I saw an elderly woman approaching up the lane She didn't notice me until she drew alongside, and this was hardly surprising because she was walking backwards She gave a little start as she saw me, but lost none of her composure "Oh, I didn't know anyone was here" I said I was sorry if I had frightened her "Oh no, it wasn't that But I only walk backwards when nobody's about I don't like to do it in public, see" I hadn't an adequate answer, so she went on, "It's my blood-pressure, you know If you have blood-pressure, you always ought to walk up hills backwards" I asked her where she had picked up this therapeutic titbit "My husband's brother's doctor—he told him to do it Wonderful difference it made to him Get up any hill now, though it's a bit slow-like"

No, she didn't *have* any trouble with traffic She could always hear it in this lane and had time to turn and face it if it was approaching from her rear—or vice-versa We parted cordially I urged her to take no notice of me, but to continue her walk in reverse, and she slowly vanished from sight up the hill, waving and nodding to the last, with only an occasional glance behind her to see that she was keeping a straight course

* * *

We are accustomed in the country to dating events by the agricultural calendar, and it is not unusual, when estimating the expected date of delivery, to be told that the last period was "in the second week of lambing time", or "just after we mowed off", or even "the day after we put the cows in the fog" We know where we are when we get sensible answers like these, but we were floored the other day when Helen came in to book her fifth She is a farmer's wife and a farmer's daughter, but her answer to the usual question was "On the day that Barbara Moore reached Land's End" Such is fame—or are we not as rural as we thought we were?

* * *

The doctor who stitched up my head told me he had a great admiration for the denomination in whose premises I had had my fall, but that he thought there was truth in all religions, and that the hope of the world lay not in the triumph of Christianity but in the World Congress of Faiths, and didn't I agree? Next morning, breakfast was hardly over before a genial ambulant patient came round to condole with me Had a fall in a church, he understood That meant that I read my Bible Could I recite the Lord's Prayer? I found I was fit enough to recite it to him, word perfect But that was not enough Did I know the real meaning of "Thy kingdom come"? Did I realise that the Second Coming was imminent? What was more, did I realise that the Bible denies there is any such place as Hell? And he left me a pamphlet for my further instruction

So if you want a quiet time in hospital, my advice is don't have your accident in a Church

* * *

When so many small rooms display the notice, "Now, Wash Your Hands", is it fair that the municipalities which minister to our comfort should demand 4*d* for a wash and brush up? After all, they cannot collect very many 4*d* s, and a free wash might save them a nasty epidemic Why not 3*d* for the brush up and nothing for the wash (and in these days of equality, let the ladies have it free too) I admit to being an obsessive hygienist, but the municipalities do administer the public-health laws

* * *

The police-inspector was quite friendly at the beginning "Just a spot test of all cars, sir" I turned the window down rather carefully as my thumb was bleeding from the last suture phial which I had opened, and I felt the cold night breeze replace the fairly strong smell of ether which pervaded my clothes and the interior of the car The inspector looked at the blood-stained tissue wrapped around my thumb and sniffed, "What is your registration number?" I wondered a bit about that Did he mean the number on the side of the engine or the number in the buff-coloured book or the number on the number-plate? I asked him "The one on the front of this car" This very deliberately and eyeing me very steadily Suddenly I was not sure I could visualise two number-plates very clearly, but could not sort out which belonged to our previous car and which to our present one In a mild panic, I found myself repeating the two combinations in a whisper and then I chose one I told him He checked "Your number-plate is so dirty, I can't see for certain" But now he seemed less suspicious and I was considering a joke or two to round off the episode, when he barked at me "What are those handcuffs doing in your car?" "Handcuffs, I haven't got any handcuffs," a bit nervously, none the less "Then whose are those?" with a triumphant flourish of his torch Even before I turned almost, I could see the handcuffs wedged in the corner of the back seat The alternatives were alarming Had I been arrested on my way to the hospital and escaped in the earlier part of the evening? Was I so absorbed in the present unsuccessful series of experiments that I had forgotten this? Had I assisted an escaped criminal, perhaps a murderer? I reached back and carefully extracted the handcuffs from the corner of the seat The metal was now soiled with blood from my thumb I tried to wipe away the blood with my clean hand The inspector, stern and uncompromising, looked at them carefully and mused "Small size, must be your youngster's" A few hours later at breakfast, my seven-year-old son casually warned me not to drive off with *his handcuffs* again, as he needed them for an emergency that very day at playtime

* * *

During a long and varied career in laboratories in different parts of the world I have often come across thirsty scientists (and other people who were just plain thirsty) trying to open bottles of beer They have been handicapped, sometimes to the point of despair, by the fact that many a laboratory lacks a bottle-opener I think, therefore, I might do my fellows a service by publishing my most important discovery The common laboratory boss (the thing that fixes a clamp to a stand, I mean, not the Prof) is the finest bottle-opener made

* * *

The final examination silly season is round again The candidate and I gazed at the skeleton as we considered the possible complications of a depressed malar bone He was a bright student and he noticed the infraorbital foramen and recognised its implications Of course the intraorbital nerve could be damaged causing diminished sensation in the upper lip I was encouraged to think he might realise the difficulties with shaving which ensue, so I persevered

"What disability could this give rise to?" Pause for thought "*Difficulty with drinking*" A further pause and then the light of knowledge dawned "Of course, difficulty with courting, sir"

* * *

MALIGNANT ANSWER

The statistical ploy of the silly old boy
who was dreadfully rude to a Cohort in Bude
(see *The Lancet* last week)* has produced not a squeak
of alarm or dismay but I feel I must say
we would go to the dogs if we gave up our logs,
as for factors like p and dx by dt,
they're essential for life if you're under the knife
or a radium bomb or a carcinotron
So, Proband, seek proof and accept the Great Truth
that statistics can't lie and that when you do die
you will very soon see your memorial will be
(and you may find this hard) just a hole in a card

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* actually, June 11 (poetic licence)

Letters to the Editor

FLUORIDATION

SIR,—Having been overseas, I must apologise for entering so late into the lists battling on the subject of fluoridation Reading through the letters in recent issues I feel that there is a very real fear that the smoke of emotional battle may cloud judgment on the evidence

The work of Ainsworth, Weaver, Forrest, Cowan, and others in this country, Pederson and Poulson in Denmark, Sellman, Syrrist, and Gustafson in Sweden, Dean, Arnold, and others in the United States, in addition to studies from South Africa, Israel, and many other parts of the world, have all established beyond reasonable doubt that there is a clear lowering of the incidence of dental decay in areas with a high natural fluoride content of the water

The evidence from Grand Rapids in the United States and Brentford in Canada, among other studies, have shown, again beyond reasonable doubt, that adjustment of the fluoride content of the water-supply to an optimum level causes approximately the same reduction in decay incidence as that found in the natural fluoride areas

Anyone viewing these facts without bias must agree that fluoridation decreases the decay-rate in the teeth of children if the fluoride is absorbed during the formative period of the teeth

Sutton[1] criticises control methods employed in some of the investigations Some of his criticisms may possibly be valid, and to be scrupulously fair and allow for possible errors one could take, say, 5% from the positive side This, however, does not make much difference when the success reported by many different workers varies between 30% and 60%, with a rough average of 50% Even Sutton does not attempt to explain away the fact that all workers, in many different lands, have reported success The striking fact is that not one single experiment throughout the world has shown that fluoridation does *not* in fact have an effect

I think, therefore, that everyone, whether for or against fluoridation, must agree after assessing the evidence that it works There are, really, therefore, only two points left for discussion (1) is it safe? (2) is the adjustment of the fluoride level of the water-supply unethical and an interference with public liberty?

To take the first point—if we are to behave as rational beings and believe in the value of evidence we are forced to the conclusion from a very large and carefully sifted volume of statistics that there is no evidence of any untoward effects from any of the high natural fluoride areas or areas in which the fluoride content of the water-supply has been adjusted, provided that the fluoride level is within reasonable bounds The upper limit of these bounds, incidentally, far exceeds the amount to which the fluoride content of the water is adjusted in experimental areas It is perfectly true that nobody knows all the possibilities I remember that years ago there was a vogue for blaming aluminium cooking utensils for an increase in gastric disorders It was not accepted as there was no sound evidence In brief, theories may wax and wane, but judgment at any particular moment must depend on the evidence available at that moment.

On the second point, we leave the realm of hard facts and enter the far more controversial one of what constitutes liberty of the subject. Any individual is at liberty to drink water from the nearest ditch if he so desires, but most of us prefer to drink water that has been treated and purified by a public authority All natural water contains fluoride to a greater or lesser extent so that in fluoridation there is no question of adding a hitherto absent salt to the water, it is merely a matter of adjusting the concentration It is perhaps not realised that the water we drink has already had a large number of chemicals added to it in the purification process, including in many instances both chlorinating agents and copper salts—both poisons in high concentration There is no such thing, therefore, as "pure" water obtainable from the waterworks, and after conversation with water engineers I believe I am correct in stating that at least twelve chemical compounds are already added to the water It does indeed seem strange that this affront to public liberty passes unchallenged when the adjustment of the level of a substance already present in the water to a level which is known to be beneficial, and which all the available evidence has been shown to be without danger, produces such an outcry

I can assure those against fluoridation that members of the Fluoridation Study Group of the Society of Medical Officers of Health and other interested bodies in this country do not take their responsibilities lightly They do try to assess the evidence fairly, while appreciating that everyone has the right to his or her own point of view No-one has ever suggested that fluoridation is the final answer to end the problem of dental decay, but if the amount of dental decay among children in this country can be reduced by nearly a half, as all the evidence suggests, much pain, misery, and mutilation could be avoided. Perhaps those who talk about ethics could balance this fact against their own personal ethical objections

School of Dental Surgery,
University of Birmingham

ALEXANDER B MACGREGOR

SIR,—Having read Dr Allen-Price's brilliant article (June 4) on the uneven distribution of cancer in West Devon I would have thought that Dr Dalzell-Ward might have paused for a moment in his determined efforts to effect micropollution of the water-supply Not that I am inferring that added fluoride causes cancer

American opinions are presumably based on American research Not everyone is satisfied that the statistical procedures in the American experiments are adequate, notably Philip Sutton in his book *Fluoridation errors and omissions in experimental trials*

Salisbury

HUGH V CAPSTICK

SUPERDOSAGE CHEMOTHERAPY OF MALIGNANT DISEASE

SIR,—The leading articles on chemotherapy of malignant disease and bone-marrow preservation in your issue of Jan 23 emphasise the advantages of superdosage of cytotoxic drugs in the control of disseminated cancer Creech's method[1] of total-body perfusion requires preliminary aspiration of bone-marrow followed by reinfusion when the effects of the drug have passed off It also requires aortic and caval catheterisation

The Westminster Hospital method of Newton[2] requires an elaborate technique of marrow freezing and precautions to avoid osmotic damage of autologous marrow during cooling and rewarming

Over the past few months, we have adopted a technique of superdosage chemotherapy which needs a minimum of apparatus and which allows us to store autologous bone-marrow safely in the patient's own tibial cavity for a period of 3–3$^1/_2$ hours

Under anæsthesia, one or both legs have a tourniquet applied at the thigh and a tiny hole is drilled into the tibial cavity in its upper third Marrow is aspirated into siliconed syringes from iliac crests and sternum, and injected immediately through the drill hole into the tibia About 80–100 ml can be transplanted, and at the conclusion of the procedure, which takes about 8–10 minutes, an otherwise lethal dose of drug is given intravenously The tourniqueted limbs are kept cold with ice

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[1] Sutton, P R M Fluoridation errors and omissions in experimental trials London, 1959

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[1] Creech, O J., Jr., Krementz, E T Ryan, R. F., Reemtsma, K., Winblad, J N *Ann Surg* 1959, 149 627

[2] Newton, K A., Humble J G Wilson, C. W., Pegg D E., Skinner, M. E G *Brit med J* 1959 i, 531

packs at a periosteal temperature of about 15°C for about three hours In this way the marrow, both transplanted and indigenous to the tibia, is stored safely until the circulating drug is fixed into the tissues or eliminated, after which the tourniquets are released and anæsthesia is discontinued

The time of tourniquet and regional hypothermia is determined by the drug used—three hours for mitomycin C, actinomycin D, and thiotepa, and 1½ hours for nitrogen mustard Complications are negligible Only transient paræsthesiæ of the foot for 24–48 hours have been noted in 4 of 11 cases with tourniquet times of 3½ hours Although hæmatological depression and gastrointestinal ulceration have occurred, there has always been adequate marrow regeneration within 24 days, as shown by peripheral blood-counts and by preoperative and postoperative assessment of marrow activity using the ^{59}Fe technique of Kramer and Wynne[3]

We feel that the best place to store marrow is in a bone-marrow cavity

New South Wales State Cancer Council,
Special Unit for Investigation
and Treatment,
Sydney Hospital, Randwick,
New South Wales

A FREEDMAN
G DAVIDSON

ADDICTION TO DRUGS

SIR,—Mr Harney (June 4) cannot reasonably complain about being misunderstood or misquoted if he repeats "misinformation" regarding the narcotic addiction problem Surely, the best means of checking false or misleading items is by stating the known facts in positive terms

He accuses me "of implying that there are no legal criminal sanctions against the abuse of narcotic drugs in the United Kingdom when there is no medical indication" I did not mention the criminal aspects of addiction at all (May 21) but stressed the fact that in the United States addiction is equated with crime whereas in the U K the emphasis is on treatment This certainly does not mean that an addict may not be prosecuted for drug offences in this country It stands to reason, however, that the person most likely to abuse narcotics would tend to be an addict He would probably be bound over on a condition of treatment rather than penalised for an offence Drug offences committed by non-addicts, although less common, are naturally regarded in a much more serious light

Mr Harney is reluctant to agree that addiction in the United States is much more a criminal matter than a medical one, but he clearly states in his letter that "coercive measures of treatment are necessary because the bulk of large city concentrations of American addicts is composed of hedonistic underworld characters" He asserts that the incidence of addiction has been reduced from 1 in 400 to 1 in 4000 in the past 45 years but he does not say whether this "good" result has been achieved by medical treatment or the activities of narcotic law-enforcement officers Presumably it is the latter

Mr Harney says I stated that addiction is spread by peddlers who are attracted by the money to be made Although I did not say that, I have no doubt that addiction is spread in this way to some extent What I did say was that as drugs can only be obtained illicitly in the United States the price is prohibitive and addicts are compelled to resort to peddling in order to find the money to pay for their own supplies I agree that the attraction is the drug and not the profit But I reassert my view that there are powerful criminal elements who exploit this situation to their considerable advantage

Mr Harney estimates that there are still 60,000 addicts in the United States, which means that the incidence of addiction is twenty times greater than in the U K But his figures are rather curious how can he reconcile a population of 175 million and an incidence rate of 1 in 4000 with a total of 60,000 addicts? My calculation would give the number of addicts as 43,750 If the figure of 60,000 is correct the incidence rate for a population of 175 million would be 1 in 2916

From time to time we have had the pleasure of welcoming distinguished visitors from America who have studied the "British method" of dealing with addiction Why is the easy lesson so difficult to learn—namely, that addiction is a matter for the medical profession?

If clinics were established where bona-fide addicts could receive injections pending their admission to hospital for a cure, trafficking in drugs would immediately become reduced and the tremendous evils associated with illicit drugging would be brought under control

London, W 1

ELLIS STUNGO
Honorary Secretary,
Society for the Study of Addiction

AMNION IMPLANTATION

SIR,—I have had many questions from doctors who have read my article of March 12 on amnion implantation, asking how to prepare the amnion

The amnion is collected fresh, straight after delivery, and stored in saline at 0° C for 4 days It is then cleaned[1] by removing mucus and staining material with cotton-wool After thorough cleaning the membrane is boiled in saline for 2½ minutes It is then stretched over a ball of cotton wool and dried in a stream of warm air It is then ready for use

The amount used for each patient is roughly 12 × 12 in. and it is cut into 4 to 6 pieces and inserted into the same amount of pockets deep in the fat of the thigh of the affected leg The wound is then closed with skin stitches which are removed on the 10th day

Acton Hospital,
London, W 3

E TROENSEGAARD-HANSEN

EFFECT OF VARIDASE ON PRESUMED CEREBRAL VASCULAR ACCIDENT

SIR,—The case recorded below may seem to have no place in a scientific journal like *The Lancet*, yet I feel it should be published

Mrs B, aged 70, collapsed on Dec 1 in a shop, complaining of agonising headache A colleague saw her and arranged for her removal home by ambulance When I visited her two hours later she was deeply unconscious

Next morning she could recognise me, speak to me, and had none of the paralysis which I had confidently expected She complained only of very severe pain in the back of her head and in her neck

Her condition remained unchanged until Dec 5 when, because of the difficulty of visiting her and having her cared for, I admitted her to the local hospital She was slightly pyrexial on admission and I prescribed chloramphenicol, which was given for five days while her evening temperature varied between 101 6° and 100 6°F On Dec 12 she was apyrexial She became incontinent of urine on that day and on Dec 13 she had a full-scale right hemiplegia with aphasia

Her general condition deteriorated rapidly and on Dec 16 a fatal outcome seemed inevitable As a shot in the dark, I prescribed one 'Varidase' tablet (streptokinase and streptodornase) four times daily Her deterioration halted Two days later she began to show some small movements in foot and hand Before Christmas Day she was able to express a wish, but not altogether clearly, to go home On Dec 26 she was able to walk with assistance and three days later she ceased to be incontinent I reduced the varidase to two tablets daily She was discharged from hospital on Jan 4

My last visit to her was on Jan 10 when there was only slight residual weakness and no neurological signs which I could detect She described herself as "able to do anything"

Because of what I left undone I cannot explain this case to myself with any confidence My idea, half-baked perhaps, is that the hemiplegia was caused by cerebral thrombosis and that the varidase acted as well as its manufacturers claim in cases of thrombosis in other sites

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[3] Kramer, H, Wynne, K H *Lancet*, 1958, ii, 1045

[1] *Brit med J* 1956, ii, 262

If I am to be shot down in flames for this view will someone please put forward another which will explain such a recovery? In more than thirty years of general practice I have seen nothing at all like it

Launceston,
Cornwall
DONALD M O'CONNOR

ŒDEMA IN "COR PULMONALE"

SIR,—I was very interested to read the stimulating and thought-provoking article by Dr Campbell and Dr Short, on the cause of œdema in cor pulmonale, in your issue of May 28 While agreeing with all they have written and realising the complexity of this problem and the multiplicity of factors that must be responsible for the œdema, I was surprised to find no mention of the possibility of a low serum-albumin as a contributory factor in the causation of œdema.

I have often noted in such patients a low serum-albumin, which I have attributed to various factors such as (1) poor food intake due to dyspnœa, (2) hypervolæmia, and (3) depressed liver function, but in only one case (a man in respiratory failure following thoracotomy for a bullectomy) did I have the opportunity to give salt-free albumin intravenously, and I was very impressed by the profound diuresis produced One case does not prove anything, but I should like to know whether others have had similar experience

Seaham Hall Hospital,
Seaham Harbour,
Co Durham
S NARIMAN

HEPATITIS AFTER INOCULATIONS

SIR,—Ever since an outbreak of jaundice in a diabetic clinic was reported during the early years of the late war, and since seeing severe jaundice in soldiers three months after intravenous antisyphilitic treatment, I have been convinced of the necessity to use a separate sterile syringe for every inoculation I felt that an explosive outbreak of serum jaundice, though not very likely, if it did occur would not be very creditable and all too explicable in the light of present knowledge

I had, however, like all R.M O s given many thousands of jabs in the Army using a variety of unsatisfactory techniques without reported ill effect

When the poliomyelitis inoculation campaign began I rejoiced that I was no longer dependent on a public authority on a war footing and persuaded my partners to buy 24 2 ml syringes

There is no difficulty nor is any large staff needed to keep these boiling in an ordinary portable spirit steriliser (ex-A.M S medical pannier type), I find that with my wife acting as receptionist and no other assistance I can inoculate 40 babies or 60 adults an hour using a separate boiled syringe and needle for each patient

It is, I know, unlikely that a boiled syringe is as sterile as an autoclaved one but at the height of the polio campaign I was myself inoculating 140 young children in an afternoon week after week—what sort of large staff would have been required to provide 140 autoclaved syringes weekly to all the doctors in a country?

Furthermore, from all accounts, sterilisation techniques are subject to error even at the centre, I would be never too happy with a peripheral service and perhaps unreasonably prefer to see the water actually boiling I comfort myself with the memory of at least one eminent and elderly surgeon removing a vast haggis of instruments in a wet cloth prior to cholecystectomy

Let us be safe but let us be simple and above all let us avoid large staffs taking in each other s washing, at least at personal-doctor level

Amble by Morpeth,
Northumberland
R P ROBERTSON

SARCOIDOSIS AND LOCAL SARCOID-TISSUE REACTION

SIR,—I read with interest the paper on the diagnosis of polymyositis by Dr Heathfield and Dr Williams (May 28) They found histological sarcoid lesions in a few cases without the evidence of *other sarcoid lesions*, and had negative results of sarcoidosis in those cases (italics mine) It appears that there is still some confusion regarding the term "local sarcoid-tissue reaction"

Histological lesions simulating sarcoidosis has been described in many organs without the evidence of generalised disease[1–3] Localised sarcoid-tissue reaction is not uncommon in muscles, and James[4] has shown that in these cases the Kveim test[5] is negative and there is no evidence of the generalised disorder

Heathfield and Williams also state (p 1160) that raised sedimentation-rate and hypergammaglobulinæmia is a feature of generalised sarcoidosis James[4] showed that only a quarter of his 200 cases had abnormal globulin patterns in the blood I have now analysed 30 patients with generalised sarcoidosis, and these findings are of interest All 30 patients were admitted to hospital for investigation and were followed up in the outpatient department or at the associated chest clinics between 1956 and 1960 These patients were divided into the following groups

Group 1 (9 cases) Bilateral hilar lymphadenopathy (B H.A) without any *clinical* evidence of sarcoidosis

Group 2 (5 cases) Erythema nodosum with B.H.A

Group 3 (11 cases) Diffuse pulmonary involvement with or without B.H A but with no *clinical* evidence of disease elsewhere

Group 4 (5 cases) Clinical evidence of generalised disease

The summary of the investigations is given below (figures in parentheses denote the number tested)

Investigations	*Group 1* (9)	*Group 2* (5)	*Group 3* (11)	*Group 4* (5)
Abnormal white count (normal 5000–10,000)	1	3	2	[illegible]
Raised E.S.R. (Westergren)	1	5	7	5
Anæmia		2	1	
Negative to 100 tuberculin units	5	1	5	1
Raised total proteins in blood (more than 8 2 g per 100 ml)	(7)	(5)	1 (8)	2 (5)
Raised globulins on electrophoresis	1 (8)	3 (5)	6 (7)	4 (4)
Raised serum-calcium (exceeding 11 mg per 100 ml)	2 (8)	1 (1)	2 (8)	(4)
Raised alkaline-phosphatase (above 14 units)	1 (7)	( )	1 (5)	3 (4)
Raised urinary calcium[6] (above 300 mg daily in men, above 250 mg daily in women)	2 (5)	( )	1 (3)	1 (1)

Most of these cases had biopsies from one or more recognised sites,[8] and the following are the results (figures in parentheses denote the number biopsied)

	Positive results				
Biopsy	*Group 1* (9)	*Group 2* (5)	*Group 3* (11)	*Group 4* (5)	*Total*
Kveim test and biopsy	5 (5)	4 (4)	7 (7)	3 (3)	19 (19)
Liver biopsy	5 (6)	1 (1)	6 (8)	3 (3)	15 (18)
Lymph-node biopsy	3 (6)	( )	5 (5)	3 (3)	11 (14)
Other biopsies	( )	( )	0 (1)	2 (4)	2 (5)

Possibly the interesting finding was the success with liver biopsy in these cases Using a Menghini needle,[9 10] there was no mortality or morbidity from liver biopsies in these patients A good correlation between the laboratory findings and clinical grouping was found

This study was possible only through the help of many colleagues Dr E Montsuchi did most of the liver biopsies, Dr D Geraint James did some of the Kveim tests Recently a reliable antigen for Kveim tests was supplied to us by Dr P Bradstreet The patients were admitted under Dr J W Craig Dr P Davies, Dr A

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1 Symmers, W St C *Amer J Path* 1957 27 493
2 Gordon G Linell F *Acta radiol Stockh* 1957, 47, 381
3 Perry D C. *Med J Aust* 1959 ii 207
4 James, D G *Quart J Med* 1959 28, 109
5 Kveim A *Nord Med* 1941 9, 169
6 Pyrah L N *Proc R Soc Med* 1958 51 193
7 Hodgkinson A Pyrah, L N *Brit J Surg* 1958 46 10
8 James D G *Brit med J* 1956 ii 900
9 Menghini G *Rass Fisiopat clin Terap* 1957, 7 [illegible]
10 Norris T S M Singh, M M Montuschi, E *Lancet* 1958 i 560

Bloom, Dr T S Norris, Dr H E S Pearson, Dr M Ashby, and Dr A L Jacobs I am very grateful to Dr D Geraint James for his helpful criticism

Whittington Hospital,
London, N 19
SAMIR K GUPTA

SOME UNCRITICISED ASSUMPTIONS IN PSYCHIATRIC THOUGHT

SIR,—There are some uncritical assumptions by Dr McConaghy (March 19) in his provocative examination of current psychiatric thinking

The dynamic therapist has by no means rejected symptom relief as an index of therapeutic success The vast majority of patients in psychiatric hospitals where dynamic psychotherapy is practised are discharged when their symptoms are relieved or at least reduced to a point where they no longer impair job, school, or family performance Dr McConaghy mistakenly identifies dynamic psychotherapy with psychoanalysis

Where the doctor, by dint of his presence in a human relationship, somehow influences the attitudes, behaviour, mood, and/or feelings of the patient, he is practising dynamic psychotherapy This treatment is based partly on the assumption that, as people have been influenced in their previous development and experience by parents, teachers, &c , so too they may be influenced in a hopefully beneficial and corrective way by a doctor who is familiar with human problems and the more subtle features of interpersonal relationships

Again few people would believe that an interpretation to a patient of the significance of his behaviour would cause any lasting or meaningful change in the patient's attitude or behaviour Interpretations are beneficial in helping patients to understand the nature of fixed habits, and perhaps to see alternative ways of dealing with life issues It is from this point that the patient may gain a greater awareness of the range of personal choices and of the opportunities which may help him to grow But the change must derive from the patient to be of any significance and cannot really be suggested by the psychiatrist

Johns Hopkins Hospital,
Baltimore, Maryland
ARI KIEV

KEROSENE (PARAFFIN) POISONING

SIR,—Dr George (April 9) states that kerosene is a mixture of various liquids and that the toxicology of some of these liquids is not known in full, while others may be anæsthetic and narcotic Therefore he considers that we should continue to encourage rapid evacuation of the ingested kerosene by gastric lavage, ignoring the danger of aspiration pneumonitis, and turning a blind eye to the considerable body of evidence which suggests that absorption of small amounts of kerosene after ingestion is a less serious problem

We should like to reply to some of the specific points raised by Dr George

(1) The commonly ingested grades of kerosene (paraffin oil) are premium (household) kerosene and regular kerosene Naphthenic acids in these grades are not likely to be found in concentrations above 0 1% and these carboxylic acids have a low order of toxicity

(2) A number of different kerosenes were studied by Deichmann [1] and all of them were found to have a low order of oral toxicity—even lower than the kerosene cited in the table in our previous letter of Jan 30 Thus, the changes in compositions which may occur in the various kerosenes have little effect on the oral toxicity

(3) There is considerable knowledge on the toxicity of the alkyl derivatives of benzene, contrary to the statement made by Dr George [2–4]

(4) There is no treatment for chemical pneumonitis Antibiotics are only of use to prevent bacterial pneumonia which may be a complication superimposed on the initial chemical pneumonitis

(5) Delay in absorption keeps the blood levels low, thus permitting storage and metabolism (detoxification) of the hydrocarbons These hydrocarbons are readily metabolised Brief high blood-levels may be more dangerous

(6) Richardson [5] studied kerosene absorption and its effects when administered to dogs and rabbits in a variety of ways—intragastrically, intravenously, by intestinal fistula, and intratracheally From this data he calculated that in a 50 lb child (aged about 7) the lethal dose would be in excess of one pint provided aspiration did not occur On the other hand, if slightly more than a teaspoonful were aspirated, severe pneumonitis, with an almost certainly fatal outcome, would result

(7) The risk of aspiration from vomiting is particularly high because of the very low surface tension which makes a small volume spread rapidly over a large area

(8) In animals the ratio of L D $_{50}$ intratracheal to oral dosage is 1 to 140

We would reaffirm our view that in the treatment of kerosene poisoning it is much safer to leave the kerosene in the alimentary tract than to attempt its removal by gastric lavage, on account of the danger of aspiration leading to pneumonitis

E H CAPEL
Chief Medical Officer
Esso Petroleum Co , London, S W 1

A WARD GARDNER
Senior Medical Officer
Esso Petroleum Co , Fawley,
near Southampton, Hants

CORPORAL PUNISHMENT

SIR,—Dr Webster (April 2) accuses Dr Waycott, by implication, of " logical fallacies " and " sentimentality " Is this really so? Is Dr Waycott's argument fallacious? And can he justifiably be called sentimental? In the same way can one not accuse Dr Webster of harshness and rigidity? Perhaps not, without being subjective

Firstly, Dr Webster makes what I consider to be a logical fallacy *par excellence* in comparing delinquent boys with Pavlov's dogs Is a delinquent boy, in his response to corporal punishment, comparable to a non-human vertebrate *in its* response to noxious stimuli under controlled experimental conditions? The boy has his whole childhood experiences, some pleasant, others unpleasant, some ego-syntonic, others ego-dystonic, some conscious and others unconscious—all conditioning, true enough, as in Pavlov's experiments—which will determine to a great extent how he will react in a given situation These early experiences (within the first six months of life especially, and certainly within the first five or six years), although in the strictest sense of the word " conditioning ", and therefore analogous to Pavlov's dog experiments, can in no logical and realistic way be compared to the conditioning stimuli in those experiments A dog does not have personality in the sense that human beings do Dogs and delinquent boys simply cannot be realistically equated in the way Dr Webster professes they can

He compares giving anæsthetics to patients for dental extractions or toenail avulsions with administering corporal punishment to a delinquent boy Did he mean that the technique of giving this punishment was unpleasant to the donor, or to the recipient? In either case his argument is invalid the doctor injecting a local anæsthetic *knows* that the end-result of his efforts is going to be success, and can do so with complete objectivity, whereas the person who does the birching of the boy does *not* know that his " treatment " will be efficacious, indeed, he may be utterly indifferent But equally well, he may be satisfying unconscious sadistic needs—this has been borne out again and again in English and American penal history What other effect can one expect but bitterness and hatred from delinquent boys when corporal punishment is indiscriminately applied? This is comparable to treating hæmorrhage from, say, the inferior mesenteric artery during a laparotomy by closing the abdomen in layers—to damming a river as it flows into the sea instead of at its source, when its banks have overflowed. One must *attack the root cause* of the delinquency, and the only way of doing this when it becomes manifest is by a psychiatric approach—psychotherapy given by *competent* therapists. It is of no use "to beat the hell out of" (a colloquialism here) the delinquents, as the Cadogan report so rightly concluded, as this builds up bitter resentment when such "treatment" reinforces old patterns of rejection. The delinquents must undergo a "corrective emotional experience"—as must all neurotics and patients with character disorders (Franz Alexander).

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[1] Deichmann, W B , Kitzmuller, K. V , Witherup, B S , Johansmann, R. *Ann intern Med* 1944, 21, 803

[2] Gerarde, H W *A.M.A Arch industr Hlth,* 1956, 13, 468

[3] Gerarde, H W *ibid* 1959, 19, 403

[4] Gerarde, H W Toxicology and Biochemistry of the Aromatic Hydrocarbons Amsterdam (in the press)

[5] Richardson, J A., Pratt-Thomas, H R. *Amer J med Sci* 1951, 221, 531

When he writes "some of us reactionaries are not very much interested in his point as to the value or otherwise of corporal punishment in constructive treatment of offenders" Dr Webster is pessimistically admitting defeat before he even starts to attempt to repair the personality of a human being heading for psychological ruin—in fact, he is "selfishly" (his own word) assisting that fellow-being in reaching such ruin.

Hospital of the University of
Pennsylvania, Philadelphia.

IAN MACKAY

SNAKEBITE

SIR,—Mrs Buckley (June 18) wants a more specific word than "poisoning", to mean snakebite. I suggest "snakebite" or, if it is fatal, "fatal snakebite". (In theory a non-poisonous snake might bite a man, but not more often, perhaps, than a man bites a dog.)

London, S.W.20

JOHN PENMAN

ADRENALECTOMY AND HYPOPHYSECTOMY

SIR,—I have read with interest the article by Mr Atkins, Mr Falconer, and their colleagues (May 28), together with the ensuing correspondence.

It seems to me that their conclusions have to a great extent clarified the position of these various operations. On theoretical grounds one might have predicted the main conclusion since the pituitary is in a sense the "traffic policeman" of the glands of internal secretion.

My purpose now, however, is to draw attention to the fact that the pituitary has been shown to be accessible via the nasal sinuses since Nager, of Zürich, gave his Semon lecture in London in 1939. Possible routes to the pituitary are via the septum, through an external incision via the ethmoid, or through the maxillary sinus and ethmoid. These routes have been used in Scandinavia and in this country, singly or in combination.

A further method of approach using the nasal bones as an osteoplastic flap, will be published elsewhere in the near future. This approach, while keeping in the midline, shortens the access and enables free use of the operating microscope.

With any of these methods of access the operation would appear to be less disturbing than either adrenalectomy or the intracranial removal of the pituitary. Furthermore the time in hospital is usually predictable and should be no longer than that needed for any patient undergoing an external ethmoidectomy—i.e., 7–10 days.

If, as seems likely, the rhinological approach to the pituitary proves to give as good results as the neurological, the practical problem noted by Atkins and his colleagues—that too few neurosurgical beds are available for this work—will to some extent be solved.

Radcliffe Infirmary,
Oxford

RONALD MACBETH

TOO MANY CALORIES

SIR,—In your excellent leading article on obesity (June 11) you refer to the contrast between the findings by Dr Duncan and his colleagues in Edinburgh[1] that methyl cellulose was ineffective in the treatment of obesity, and my finding[2] that it was effective. I am writing to draw attention to some of the differences in these two sets of experiments, one or more of which may account for the different results.

Firstly, there were clearly differences between the type of patient. The Edinburgh patients are rightly called "refractory", and the controls without drugs did not lose weight significantly during the experiment, my control patients lost six pounds in six weeks. Secondly, the Edinburgh workers gave 4.5 g. methyl cellulose daily, compared with the 9 g. which I gave. Thirdly, the preparation used in Edinburgh was in the form of tablets, which do not swell to the same extent as the powdered methyl cellulose used by me.

It is then reasonable to conclude that at least some obese patients will find it useful to take methyl cellulose, provided they take sufficient and it is in the powder form.

Queen Elizabeth College,
London, W.8

JOHN YUDKIN

THE PERSONAL DOCTOR

SIR,—Dr Fox, in *The Lancet* of April 2, writes that attracting the younger practitioner to the country is a difficult matter in the United States. This is not, in my experience, completely true.

While it may well be that many rural areas are "under-doctored", a large fraction of my own generation (class of 1942) have already established themselves not only in the suburbs but also in "exurbia". Older men and younger men, too, are moving out of the cities. As a matter of fact, one of my teachers in medical school moved his practice from Brooklyn to the remote suburbs on Long Island long after I had left the City of New York permanently. As this man was a chief of service in one of Brooklyn's outstanding voluntary hospitals, and a specialist certified by an American specialty board, one can scarcely regard his removal as reflecting any sort of failure or maladjustment on his part. Indeed, I hear that his old hospital in Brooklyn is trying to lure him back.

As for myself, I could not afford to bring up my five children, as I do now, in New York, even if I could maintain my present income in the city. The assumption that I could maintain my present income in New York, or in any other metropolis, is utterly unfounded (I am a pathologist). Further, I could not enjoy the freedom of directing my own laboratory without lay interference, as I do here. A metropolitan hospital would never give up control of the laboratory's purse strings. This, by the way, is very much the case at the Hunterdon Medical Center, where the pathologist's share of laboratory income goes into the group's treasury, rather than into the hospital's pocket. The result is that both the Hunterdon pathologist and I need not battle any sort of bureaucracy for needed funds. (I happen to know Hunterdon because we are the hospitals closest to each other in New Jersey, because the pathologist there and I have had training in the same institution, and because the pathologist and I are old friends who "cover" for each other often.)

There is a great deal of interesting information in Dr Fox's article, much of it new to me. I think, nevertheless, that it fails to point out an important aspect of the lack of physicians in rural areas. That is the failure of the small community to meet the needs of modern practice. Once it does so, physicians will leave the "rat-race" of the big city, these physicians will be well-qualified specialists as well as generalists. The example of Hunterdon has been cited. Warren Hospital, its closest neighbour, in Phillipsburg, New Jersey, has no medical-school affiliation or support from funds or foundations (save for the building fund, raised by public subscription, *locally*) It is a 200-bed hospital There are fully qualified general surgeons, ophthalmic surgeons, obstetricians and gynæcologists, orthopædic surgeons, pædiatricians, internists, otolaryngologists, and urologists, as well as generalists on the active staff There are available neurosurgeons, thoracic surgeons, dermatologists, and neuropsychiatrists, who are nearby and fully qualified, as consultants (with appointments to the consulting staff of the hospital)

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[1] Duncan, L. J. P., Rose, K., Meiklejohn, A. P. *Lancet*, June 11, 1960, p. 1252.
[2] Yudkin, J. p. 1135

This must, to a great extent, be attributed to the hospital board's foresight in making full-time appointments in three departments anæsthesia, pathology, and radiology In order to make these appointments a reality, they must offer the appointees enough professional independence (as well as mere financial gain) to attract them from the security of the larger institutions All three of these specialists do a great deal more work in hospitals such as Hunterdon or Warren than would be expected of them in New York, Boston, Philadelphia, or Chicago, where small armies of specialists man these departments, and where the specialties are subdivided (e g , diagnostic and therapeutic radiology, or morbid anatomy and clinical pathology)

Of course, all is not perfect, either at Warren or at Hunterdon, but the good so far outbalances the bad that neither Hunterdon's pathologist nor I is seeking another appointment The opposite is, to my personal knowledge, the case in several New York hospitals

Phillipsburg,
New Jersey

PAUL DE R KOLISCH

CLOSING MECHANISM OF THE FEMALE URETHRA

SIR,—In his letter of April 2 (p 770) Dr Vantrappen explains the statement of Mr Goldberg (March 19) that when the lower œsophagus is above the diaphragm its sphincteric function fails With inspiration the intrathoracic pressure decreases and the intra-abdominal pressure increases, thus resulting in a fall of pressure from the stomach to the part of the œsophagus above the diaphragm If, however, the lowest part of the œsophagus is below the diaphragm an inspiration would increase its pressure to the same extent as it would increase the pressure of the stomach, and there would be no reason for reflux of gastric juice This explanation has caught my interest, since I have found that the same closing mechanism controls another outlet from the abdominal cavity—the female urethra

The fact that the urethra can be penetrated from the outside into the bladder with a pressure no higher than 100 cm of water, whereas a cough may increase the pressure within the bladder to as much as 250 cm of water without normally causing leakage, points to the possibility of the upper urethra being functionally within the abdominal cavity If it were, a cough would increase the pressure within the upper urethra to the same extent as within the bladder, and there would be no stress on the sphincter function of the urethra To testify this hypothesis 100 women (50 without urinary complaints, 25 with stress incontinence, and 25 who had had their first delivery six days earlier) were examined with simultaneous recording of intravesical and intraurethral pressure A double catheter, 25 cm long and with an outer diameter of 1 9 mm , was used From the apex of the catheter the intravesical pressure was lead to an electromanometer, and from a balloon of thin rubber 6 cm from the apex the intraurethral pressure was lead to another electromanometer (fig 1) The pressures were recorded with a two-channel Elema Mingograph

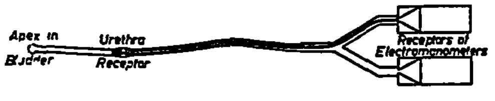

Fig 1 —Measurement of intravesical and intraurethral pressures

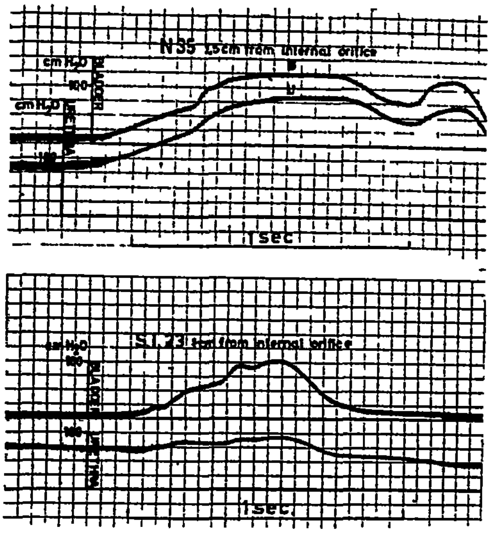

Fig 2 —(a) Normally (N 35) the intravesical as well as the intraurethral pressure is increased by a cough; (b) in stress incontinence (S 1 23) the difference between intraurethral and intravesical pressure becomes zero

During the examination the patient was lying in the lithotomy position The bladder was filled with 250 ml of saline solution, the catheter was introduced and then stepwise withdrawn, 0 5 cm at a time In every position of the catheter the intravesical and the intraurethral pressures were simultaneously recorded, both when the patient was asked to relax and when she was asked to cough vigorously With this method it was found that when the normal woman relaxes, the pressure in the two upper thirds of the urethra was from 50 to 150 cm of water When a cough increased the pressure of the bladder, the pressure in the upper urethra was simultaneously increased and therefore the intraurethral pressure remained considerably higher than the intravesical pressure In stress incontinence, however, a cough did not increase the intraurethral pressure to the same extent as the intravesical pressure, and, in the moment when incontinence was manifested, the difference between these two pressures was zero (fig 2)

Sabbatsberg Hospital,
Stockholm,
Sweden

GORAN ENHÖRNING

EXPIRED-AIR RESUSCITATION

SIR,—I have been following this correspondence with interest, and should like to make a few remarks

Many lives have been saved in Sweden, some of them by children, since the technique of expired-air resuscitation was demonstrated on television two years ago The "patient" was not a dummy but a curarised anæsthetist This film has been rebroadcast, and must by now have been seen by a very large number of people Recently a man kept his wife alive during acute respiratory obstruction (due to retrosternal thyroid adenoma) until she could be got to hospital, he had no special training, and merely did what he had seen on television This case also illustrates a unique feature of the technique by no other method of artificial respiration can the inspiratory pressure be raised and an obstruction forced, and no other method would therefore have been of any use in this case

The name "expired-air resuscitation" is, of course, the most appropriate one, but I believe that the lay rescuer is helped by the simple term "mouth-to-mouth breathing", which is used in this country, because it tells him exactly what he has to do in the heat of the moment

The objections that have been raised on æsthetic grounds have proved to be theoretical there is no hesitation when the need arises

The method is this year being adopted officially by all authorities throughout Sweden—a country where drowning is common

Uppsala, Sweden. MARCIA SKOGH

PAY INCREASE TO MEDICAL SUPERINTENDENTS

SIR,—The proposed increase of £250 per annum to mental hospital superintendents appears singularly inappropriate at a time when the new Mental Health Act is hoped to stimulate experimentation in medical administration It will be recalled that this increase in remuneration was recommended to the Royal Commission by the Medical Superintendents' Association but was not supported by the British Medical Association, the Royal Medico-Psychological Association, or the Central Consultants and Specialists Committee

In the hospital of the future we can expect psychiatric units to be linked with general medical and surgical units, and the medical superintendent, if any, may as likely be a surgeon or a physician as a psychiatrist The conditions, therefore, under which this pay award was recommended for medical superintendents of mental hospitals now no longer seem to exist and its implementation, therefore, becomes irrelevant

London. A J OLDHAM

COMPARISON OF CEREBRAL FAT AND AIR EMBOLISM

SIR,—The case of cerebral fat-embolism reported by Harnett et al[1] has many features in common with air-embolism, and a comparison between the two conditions may be of interest, especially in relation to treatment and prognosis Moreover, it seems desirable to record, for its own sake as well as for comparison, the following case which occurred in 1952 as a complication of extrapleural pneumothorax

A girl, aged 18, had cerebral air-embolism while sitting up after receiving a 150 ml refill of an extrapleural pneumothorax Half a minute after completion of the refill, she suddenly fell back She was found to be unconscious and was, having right-sided convulsions Her face was extremely pale, the pulse was impalpable at the wrist, and respirations were shallow and jerky

In this patient, and in the girl with fat-embolism described by Harnett et al, embolism resulted in deep coma, though with fat-embolism consciousness did not return for two to three weeks, compared with thirty-six hours in the air-embolism case

The clinical features in both cases suggested widespread focal lesions in the brain There was deviation of the head and eyes to the left, and gross spastic paralysis of arms and legs, less complete on the right than on the left This distribution is to be expected in air-embolism in a sitting patient, because the bubbles would tend to go up the right innominate and common carotid arteries There would be a similar though weaker effect with buoyant emboli where a patient was supine Experiments with dogs have shown that in arterial air-embolism, the site of ischæmia is determined by the principle of air buoyancy[2]

Voluntary muscular activity began to improve in the fat-embolism case during the fourth week, and in the air-embolism case on the fourteenth day, at which time also sensation of pain was appreciated again in the upper limbs

A year after the occurrences, the main features may be described under two headings

Central nervous system —The fat-embolism patient still had slight spasticity of the lower limbs and impaired cutaneous sensation along the outer border of the right foot In the air-embolism patient, the right upper and lower limbs were apparently normal The muscular power of the left upper and lower limbs was estimated as being 75% normal in the main, but with residual foot-drop, wasting of the interossei, and wasting of the thenar and hypothenar eminences Knee and ankle jerks were still spastic and muscle-joint sense appreciation was variable

Mentality —The fat-embolism patient had previously been rated as average and was now regarded as being possibly "dull normal" The mother agreed that personality and behaviour recovery was remarkably complete, though some of the previous traits were now more pronounced The parents of the air-embolism patient considered that there was no deterioration in her intelligence The mother reported spontaneously that the experience must have done the patient some good before she had been difficult and moody, but was now much happier and contented

Further progress in the fat-embolism case was not recorded Three years after the embolic episode the air-embolism patient continued to improve The muscular power of the left upper and lower limbs was almost normal, though there was still wasting of the interossei and the eminences She could now walk without a limp, though slight foot-drop was apparent when she ran Knee and ankle jerks were normal and muscle-joint sense had definitely improved

Electroencephalography —Fat-embolism suggested "multiple diffuse emboli scattered through the brain substance, probably most concentrated in the left temporal area" Air-embolism E E G was not performed until seven weeks after the embolic episode when the report was "mild generalised dysrhythmia with frequent outbursts of theta and some random delta activity There is no evidence of focal brain damage" Serial E E G examinations of a similar case[3] showed obliteration of normal cortical activity with gradual return towards normal

The air-embolism patient was examined by a neurosurgeon ten days after the embolism His opinion was that, in the normal course of events, very little improvement could be looked for from such extensive lesions in the central nervous system Roessle[4] reported that, where the patient survived, no abnormality could be detected at subsequent necropsy, even when scarring would have been expected

The girl who had the fat-embolism was last described as being more-or-less her previous self When last seen, the air-embolism patient was also leading a normal life, had married and become pregnant

The following may also be of value in treatment

Posture —The head should be lowered to reduce the likelihood of bubbles travelling up the carotid arteries Banyai[5] recommended that the patient must "practically be stood on his head" The patient should probably be positioned midway between the prone and left lateral position in an attempt to bypass the openings of the carotid arteries This position will also relieve any obstruction due to air-lock in the outflow tract of the right ventricle if the air has entered via the systemic venous system[2]

Analeptic —A cardiorespiratory stimulant is usually needed to combat the effect on the vital centres In view of the acuteness of the condition the intravenous or intracardiac route is recommended

Oxygen —Oxygen should be given as soon as possible and continued Kelly et al[3] reported that the continuous breathing of oxygen caused substantial improvement in paralysis even though its use had been delayed for three days

Cerebral vascular dilators —In view of the vascular spasm associated with air-embolism, cerebral vascular dilators may be of value, but the individual emboli result in infarct-like and necrobiotic areas of cerebral matter and focal hæmorrhages, so that a vascular dilator would aggravate this tendency and outweigh any initial benefit The air-embolism patient was treated with posture, intracardiac stimulant, and oxygen, but no vascular dilator

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[1] Harnett, R W F Paterson, J R S, Lowe K G, Stewart, I M, Uytman J D *Lancet*, 1959 ii 762

[2] Durant, T M Oppenheimer M J, Webster, M R, Long, J *Amer Heart J* 1949, 38 481

[3] Kelly, H G, Gibson W C Meakins J F *Canad med Ass J* 1947 5 388

[4] Roessle, R *Virchows Arch* 1948 315, 461

[5] Banyai A L Pneumoperitoneum Treatment London 1946

In cerebral fat and air embolism initial and prolonged follow-up treatment becomes all the more important when one realises how remarkable the clinical recovery may be even after severe coma and paralysis

I am grateful to Dr A S Hutcheson, consultant chest physician, Argyll Area, for criticism of this report

County Sanatorium,
Oban, Argyll
PETER MACPHERSON

TRIAL OF A NON-SPECIFIC ANTI-CATARRH VACCINE

SIR,—Treatment of chronic respiratory infection, with persisting cough and dyspnœa, is disappointing, especially in the established stage of the disease Acute exacerbations are often preceded by an upper respiratory infection which spreads to the chest Each attack leaves the patient worse, so it is desirable to prevent such upper respiratory infection The use of broad-spectrum antibiotics has become popular,[1–5] but is expensive

Ritchie[6] reported favourably on the use of an autogenous vaccine in the prophylaxis of the common cold, and he believes that most effects are caused by the relatively enhanced virulence of the patients' normal nasopharyngeal flora after depression of resistance by the virus Unfortunately the giving of autogenous vaccines on a large scale is not practicable The effect has been tried of a specific anticatarrhal vaccine on a group of patients with recurring respiratory infection

Each ml of vaccine contained

Neisseria catarrhalis	50	million	organisms
Bacterium pneumoniæ	50	„	„
Hæmophilus influenzæ	250	„	„
Streptococci	25	„	„
Pneumococci	250	„	„

Patients were given 0 25, 0 5, and 1 ml subcutaneously at intervals of seven days, starting in the autumn of 1958, and continued with 1 ml at monthly intervals until March, 1959 Not all had the full course

The injections were given as part of the work of an asthma injection clinic Patients were allocated to treatment and control groups (who received sterile water) by the clerk arranging appointments for injection, so the physician ordering the vaccine did not know if the patient would receive it It had been proposed that 1 patient in 4 should be a control, but it was found that of patients who did not attend for the first injection more had been allocated to the control group In all, 79 received the vaccine and 15 sterile water (see table I)

TABLE I—AGE AND SEX DISTRIBUTION OF THOSE RECEIVING THE VACCINE AND STERILE WATER

Age	Controls		Recurrent respiratory infections	
	Male	Female	Male	Female
0–14	4	3	12	11
15–34	0	2	6	6
35–54	1	1	12	16
55+	1	3	3	13
—	6	9	33	46

The results were assessed in May and June after the course was complete, and we studied the record cards of the injections with the noted replies to questions on progress at each visit Those reporting no acute exacerbation or only one or two colds through the winter, with no bronchitis, were classed as a good result Those reporting no benefit were classed with those who reported slight improvement on previous years The results are given in table II, with males and females combined since no sex difference was found There is no significant difference between the controls and those receiving the vaccine

TABLE II—RESPONSE TO TREATMENT

—	Controls	Recurrent respiratory infections
Good result	3 (20%)	20 (25 3%)
Moderate improvement	4 } 11 (73 3%)	30 } 56 (70 9%)
Stationary	7 }	26 }
Worse	1 (6 6%)	3 (3 8%)
—	15	79

Patients with chronic bronchitis and parents of catarrhal children appreciate fresh interest and attempts to ease their troubles. They are, therefore, probably reporting greater improvement than has actually occurred. Psychological factors were also probably responsible for the reactions reported 2 patients who received the vaccine reported "colds" for 24–48 hours after each injection, while 3 of the controls reported tightness of the chest after each injection of sterile water

The difference in results in non-specific and autogenous vaccines may be accounted for in the very heterogeneous nasopharyngeal organisms of the general population Unfortunately laboratories are not willing to make autogenous vaccines The organisation of the injections was not difficult and attendance was good, even in bad weather Patients with recurrent chest infections will go to considerable trouble in pursuit of something they hope will help

Trial of this non-specific anticatarrhal vaccine as a prophylactic against recurrent chest infection has shown it to be useless

Harrow Chest Clinic,
Middlesex
J B CLARK
R GRENVILLE-MATHERS

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1 Helm, W H, May, J R, Livingstone, J L *Lancet*, 1954, ii, 630
2 Helm, W H, May, J R, Livingstone, J L *ibid* 1956, i, 775
3 May, J R, Oswald, N C *ibid* 1956, ii, 814
4 Moyes, E N, Kershaw, R A *ibid* 1957, ii, 1187
5 Edwards, G, Fear, E C *Brit med J* 1958, ii, 1010
6 Ritchie, J M *Proc R Soc Med* 1958, 51, 273

RELIEF OF PAIN IN RESPIRATORY FAILURE

SIR,—We have been interested for some time in the problem of management of pain in patients with respiratory failure It is generally agreed that the most effective drug —morphine—is contraindicated because of its depressant effect on the respiratory centres. When pethidine was introduced in 1939 it appeared to be the answer to the problem, but it has since been shown that when given in a comparable analgesic dose the drepessant effect is similar[1 2] Recent experience in anæsthetics and obstetrics has shown that mixtures of pethidine and a small dose of a narcotic antagonist (levallorphan) cause less respiratory depression than pethidine alone[3–7] Hossli and Bergmann,[8] using such a mixture to treat postoperative pain, showed that the analgesic effect is in no way impaired

The use of a proprietary mixture 'Pethilorfan' (Roche) containing pethidine and levallorphan in the proportion of 80 to 1 for the relief of pain in a number of respiratory cripples impressed us favourably, both with regard to its analgesic action and apparent freedom from respiratory depression We decided to determine objectively the effect of this mixture on respiration by repeating respiratory function tests one hour after injection (containing pethidine hydrochloride 100 mg and levallorphan tartrate 1 25 mg) in a consecutive series of patients admitted for the investigation of respiratory failure who were undergoing routine physiological assessment The mean values and standard deviations in this small series of 12 patients are recorded in the accompanying table

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1 Prescott, F, Ransom, S C, Thorp, R H, Wilson, A *Lancet*, 1949, i, 340
2 Loeschcke, H H, Sweet, A, Kough, R H, Lumbertsen, C J *J Pharmacol* 1953, 180, 376
3 Lloyd, T S *Va med Mon* 1956, 83, 551
4 Roberts, H, Kane, K M, Percival, N, Snow, P, Please, N W *Lancet*, 1957, i, 128
5 Hunter, A R *Brit J Anæsth* 1958, 30, 233
6 Foldes, F F, McNall, P G, Koukal, L R, Tanaka, R *Anæsth* 1959, 14, 255
7 Posner, A C *Brit med J* 1960, i, 124
8 Hossli, G, Bergmann, G *Schweiz med Wschr* 1959, 89, 863

EFFECT OF PETHIDINE-LEVALLORPHAN MIXTURE ON RESPIRATORY FUNCTION

—	Respiratory-rate per min	Tidal air (ml)	Minute volume (litres)	P E F.R	Arterial blood-level	
					O_2 (vols %)	Co_2 (vols %)
Mean value before injection	17 5 (±*5 23*)	783 3 (±*436 6*)	11 68 (±*2 60*)	159 58 (±*21 27*)	15 15 (±*3 37*)	45 31 (±*5·41*)
Mean value after injection	20·5 (±*8 06*)	755 8 (±*450 6*)	12 48 (±*2 11*)	170 83 (±*22 75*)	15 06 (±*3 26*)	45 70 (±*6 08*)
Difference between mean values	+3 0	−27 5	+0 8	+11 25	−0 09	+0 39

Figures in parentheses = standard deviation.

The figures suggest that there was improvement rather than depression of respiration following the use of pethilorfan, but analysis using the "t" test shows that the changes are not statistically significant Nevertheless it is clear that the respiratory depression known to follow the use of pethidine did not occur

A mixture of pethidine and levallorphan in the proportion of 80 to 1 seems to be a desirable substitute for morphone or pethidine alone in the treatment of pain in patients with severe respiratory disease, and since no reference in the literature can be found for this use of the mixture we hope that our findings will be of interest

Industrial Chest Unit,
Bangour Hospital,
West Lothian

T G JUDGE
J H ROLLAND RAMSAY
C KELMAN ROBERTSON

FRACTURES OF TIBIA AND FIBULA

SIR,—The method of holding certain fractures of the leg over wedges described by Mr David Thomas in your issue of June 4 is not new, having been described by Mr E A Nicoll of Mansfield some years ago, but it is, like all simple procedures, an excellent method in practice Many transverse fractures of the tibia are so stable after reduction that only the one wedge under the knee is needed if the leg is allowed to fall into external rotation

Ashford Hospital,
Ashford, Middlesex

F GODSALVE WARD

GRANTS TO STUDENTS

SIR,—It was to be hoped that having raised the subject of university awards in your annotation Backed by the Community (June 18), you would have found it possible to express an outright opinion in favour of the abolition of the present parental means test This measure particularly hits members of our profession who work harder than most others and have a struggle to maintain a standard of living proportionate with our efforts and responsibilities After paying income-tax and perhaps surtax, we now have in many cases to pay full university fees, board, &c, even although our children may be clever enough to qualify for a State scholarship The net result is to double-tax our incomes and we end up a good deal worse off than the "less fortunate" in the so-called lower income groups

Many parents in present circumstances cannot afford to send more than one child to university Other children equally talented suffer through no fault of their own and it is probable that the nation can ill afford to lose them Your remarks about other ladders will not convince many

One has heard of young men who have got to university only through the death of their fathers, this making them eligible for a grant This is a sad commentary on the present system Mention the word "means test" to some of our political friends and they almost have apoplexy—but of course this is different

The abolition or at least drastic reform of this system is more important to the majority of middle-aged and young doctors, who have or will have children to educate, than any amount of controversy over drugs for private patients or possible methods of allocation of merit awards

Middlesbrough

B H ELLIS

*** The Committee on University Grants was divided on the abolition of parental contributions In our annotation we tried to summarise the case put forward by each group (The phrase "some other ladder" is a quotation from p 56 of the report) Our feeling that these contributions should be abolished is longstanding (*Lancet*, 1958, i, 1286) —ED L

ÆTIOLOGY OF KURU

SIR,—A number of recent publications in *The Lancet* and other journals have left the impression that the evidence is very strong for a genetic ætiology of kuru, a fatal degenerative disease of the central nervous system found among the Fore tribe of New Guinea, in spite of the cautiousness of the investigators in stating a hypothesis of genetic ætiology only tentatively Kuru has been said largely to attack children and adult females, while rarely attacking adult males

The negative evidence for the genetic ætiology of kuru is considerable and has not been stressed Stated briefly, such negative evidence is

(1) Women from kuru-free groups have acquired the disease after marrying into the Fore tribe [1]

(2) The mutation-rate required to explain such a high frequency of the disease in the population is much greater than the known mutation-rates for other pathological genes Investigators say that as much as 1% of the population was suffering from the disease during a period of investigation lasting for several months The disease usually runs its fatal course in eight to nine months

(3) Data from one publication [2] indicate that of 33 maternal grandmothers of kuru victims, 15 died of kuru, while of 31 paternal grandmothers of victims, only 2 died of the disease If, as the investigators have suggested, the male heterozygotes carry kuru without expressing it, while female heterozygotes are victims in adulthood, then children should be at least as likely to get the gene from their father as from their mother, and in turn from their paternal grandmother as their maternal grandmother This occurrence of the disease among grandmothers has a probability of happening by chance less than once in a thousand times

(4) In an early publication Gajdusek and Zigas [3] give some indication that the disease may be of recent origin At a later date, Klatzo et al [4] give the impression that the disease has been present for a long time If there is any possibility that the disease is recent, the issue must be settled before the genetic hypothesis can be accepted, since the frequency of the disease in the population is too great to be accounted for by a disease of recent genetic origin

(5) A few alleged recoveries are reported [5] If there are recoveries, a genetic explanation would seem unlikely

With our present knowledge of genetics, we cannot accept kuru as a genetic disease unless it can be shown, as some of the investigators have argued, that an extremely unstable chromosome locus along with, perhaps, a mutagenic factor exists in the Fore environment, or that some selective advantages which have not yet been identified are working in the reproductive favour of individuals carrying the kuru gene One of the important problems in the investigation of the genetic ætiology of such a dis

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1 Gajdusek, D C, Zigas V *Amer J Med* 1959, 26, 461
2 Bennett, J H, Rhodes F A, Robson, H N *Amer J hum C* 11, table 11, p 184
3 Gajdusek D C, Zigas, V *Amer J Med* 1959 26 461
4 Klatzo, I, Gajdusek D C, Zigas V *Lab Invest* 1959 8
5 Gajdusek, D C, Zigas, V *Amer J Med* 1959, 26, 450

would be to identify the large number of male heterozygotes who would have to be carrying the gene, and to show beyond a doubt that they can pass on the gene to their progeny

On the other hand, the Fore society presents such a clear-cut possibility for an environmental agent to attack women and children and by-pass adult males, that it would seem difficult to abandon the possibility of an environmental ætiology resulting from a toxin, virus, or deficiency The anthropological investigations of Berndt[6] indicate that, if there is one significant fact about Fore society, at least up to the recent past, it is the marked separation of men on the one hand and women and children on the other, in almost every phase of life, including dwelling houses

School of Tropical Medicine and
Public Health ANN FISCHER
Department of Sociology and
Anthropology, Tulane University,
New Orleans, Louisiana JOHN L FISCHER

A CHLOROFORM SYNDROME?

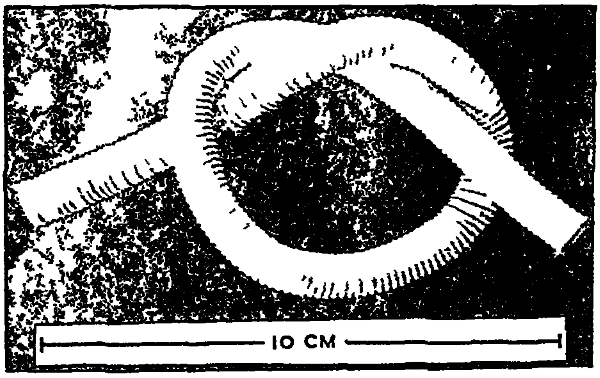
SIR,—From continued observation of a case which has come to my notice it seems that there is a "chloroform syndrome" Repeated exposures to this inhalant anæsthetic for eighteen months or more have gradually produced symptoms and clinical signs which may indicate (1) an individual hypersensitivity to the material, (2) a toxic effect primarily on liver, kidneys, and myocardium, but also affecting the pituitary and suprarenal, or (3) a more specific ganglion-blocking or even cell-destructive effect on sympathetic ganglia and chromaffin tissue A year or more may elapse before the case can be presented in full for publication

Meanwhile, Sir, may I ask for details of cases and/or the views of your readers who have come across any untoward effects following repeated exposure to chloroform vapour?

*59, Walnut Tree Walk,
London, S E 11* H A L O LATTA

A NEW ARTERIAL PROSTHESIS

SIR,—A new type of arterial prosthesis (see figure) has recently become available It is of British design and manufacture, being made entirely from Courtaulds high-melting-point polyethylene fibre (Courlene 'X3')



In order to provide flexibility and slight elasticity, it is woven in the form of a double helical spring and may be autoclaved if the temperature during this process is not allowed to exceed 118 C, boiling or cold sterilisation with any suitable solutions are alternative methods of preoperative preparation The prosthesis must be divided with the cool cautery in order to seal the fabric, but this done, the ends of the tube provide a powerful hold for sutures Pre-clotting of the prosthesis is desirable

Extensive experimental investigation of these synthetic grafts has been carried out Courlene X3, being a pure polyethylene, causes minimal tissue reaction and loses none of its strength after periods of over 12 months in the body—factors which might be anticipated from its chemical constitution

These prostheses are made by P Davenport Ltd (Macclesfield) and are now available through the Genito-Urinary Manufacturing Co Ltd

Department of Surgery,
The University,
Sheffield B N CATCHPOLE

CONFIRMATORY MEDICAL CERTIFICATE BEFORE CREMATION

SIR,—I endorse Dr Hinden's criticism (June 18) of the inadequacy of the confirmatory medical certificate in regard to question 3 which asks "Have you made a post-mortem examination?" This is, however, but one of several shortcomings of the statutory form which has led me recently to inquire to what extent an individual cremation authority may be enabled to revise it

There is, for instance, the question on Form B relating to the inspection of the body after death which asks "What examination of it did you make?" This elicits an extraordinary variety of answers few of which are of material assistance to the referee There is also a lack of any suitable question which enables a practitioner to insert helpful information in regard to clinical history in support of the stated cause of death

It is, of course, very much easier to point out the inadequacy of a form than to devise a new one, but I would have little doubt that a panel of medical referees could draw up something much simpler and more to the point than the existing one

It seems possible in the meantime for cremation authorities to make provision for additional information to be given, but it would not appear possible for the statutory questions to be altered in any way without amending legislation

K O A VICKERY
Medical Referee,
Eastbourne Eastbourne Crematorium Authority

SIR,—Has it occurred to Dr Hinden that the person best qualified to sign the second part of the cremation certificate is the pathologist performing the autopsy?

Pathological Laboratory,
Southlands Hospital,
Shoreham-by-Sea, Sussex K S RODAN

SIR,—I entirely agree with Dr Hinden In answer to question 3 "Have you made a post-mortem examination?" "Not personally, one performed", should suffice At least it would tell the medical referee that a post-mortem was carried out

Manchester I A KELLOCK

SIR,—There is an easy way out for Dr Hinden The pathologist who has performed the postmortem is the best person to complete the second medical certificate

In addition, it has been recommended that the second certificate should be given by a person other than one who has had the deceased in his care

Cardiff R C R CONNOR

SIR,—May I suggest two solutions to Dr Hinden's problem? He could ask the morbid anatomist to complete the confirmatory certificate, or he could visit the post-mortem room and have a look at the findings I am sure the morbid anatomist would make Dr Hinden welcome and assist, if necessary, in interpretation Dr Hinden would then be correct in saying that he had performed a postmortem examination. A knife is useful in exposing organs for examination and helps to determine consistency, but one can examine with one's eyes.

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[6] Berndt, R M *Sociologus*, 1958, 8, 4

The Radcliffe Infirmary, Oxford R. H. COWDELL

Parliament

QUESTION TIME

"Spiritual Healers" in Hospital

MR KENNETH ROBINSON asked the Minister of Health what guidance he had given to hospital management committees regarding the admittance of members of the National Federation of Spiritual Healers into hospitals for the purpose of treating National Health Service patients, and how many management committees permitted these activities at the present time.—Mr DEREK WALKER-SMITH replied: I have not given guidance to hospital management committees, as I consider on present advice that the visiting of patients is a matter which should be left to the hospital authority's discretion, in the light of the views of the doctor in charge of the particular patient who has asked for the visit. While I do not know the practice of individual committees, they are generally aware of my view.

Dr DONALD JOHNSON: Is the Minister aware that the Federation of Spiritual Healers are making extensive claims in this matter and are saying that they are entering hospitals to give treatment by permission of the regional hospital boards? Does he not agree that, if this is so, it is a matter for his decision and not one to be left to the regional hospital boards? We look to him for guidance and a decision in the matter.—Mr WALKER-SMITH: I have no responsibility for any claims made by this Federation or any other body. There are two requisites here: first, that the patient must ask for any such visit before it can be contemplated, and, secondly, that the hospital authority must exercise its discretion with due regard to the views of the doctor in charge of the case.

Mr ROBINSON: I do not want to express a view one way or the other about the merits of the Federation, but does not the Minister think that this is a matter in which he should give guidance to hospital authorities rather than leave the decision to individual authorities? Is he aware that these healers are now reported to be present in 50% of the hospitals run by management committees?—Mr WALKER-SMITH: If I am right as to the factors governing these cases, it must always ultimately be a matter for local decision, in the light of these factors. Therefore, general guidance, beyond what I have already said, would not appear to be appropriate. Dr EDITH SUMMERSKILL: Did I understand the Minister to say that a regional hospital board can make a decision in favour of these visits but that a doctor can refuse only in a specific case? Can a doctor refuse to have a spiritual healer attending any of his cases on the ground of principle?—Mr WALKER-SMITH: The question does not arise in the first place unless and until the patient concerned asks for the visit. That having been done, it is a matter for the discretion of the hospital authority whether or not the visit will be sanctioned. In coming to that decision the hospital authority will give due weight to the opinion of the doctor in charge of the case.

Tests for New Drugs

Mr GEORGE DARLING asked the Minister if he would introduce regulations to require that all new drugs be tested and evaluated by a responsible body before they are offered for sale to the public.—Mr WALKER-SMITH replied: While there are no existing powers under which such regulations could be made, I am giving, and will continue to give, all the help and encouragement I can towards improvements in the present arrangements and facilities for clinical trials. The Central and Scottish Health Services Councils have agreed to extend the terms of reference and membership of the Standing Joint Committee on the Classification of Proprietary Preparations to enable this committee to assist.

Obituary

ALEXANDER KENNEDY

M.D. Lond., F.R.C.P., F.R.C.P.E., D.P.M.

Dr Alexander Kennedy, whose death on June 11 we announced last week, had held the chairs of psychological medicine at Durham and Edinburgh. He came to both departments at a time of reorganisation, and perhaps his chief contribution to psychiatry was the development of these professorial units in the light of his own ideas, and the integration of the teaching of psychiatry with the other disciplines of medicine.

Feature Press Photo Agency

He was born in 1909 and was educated at the City of London School and St. Thomas's Hospital, where he qualified in 1932. After holding house-appointments there he took his M.D. and the M.R.C.P. in 1934 and specialised initially in pædiatrics. He continued his postgraduate studies at the Johns Hopkins University, and in 1936 he was awarded a Rockefeller travelling fellowship in neuropsychiatry. On his return to this country he became medical officer in charge of the children's department at the Maudsley Hospital, while the present children's hospital was being built with the assistance of the Rockefeller Foundation. In 1938 he was awarded the gold medal of the Royal Medico-Psychological Association. During the late war he carried out research into the psychology of parachute and commando training and took part in operations in the Western Desert, Crete, Greece, and Yugoslavia. Later, with the rank of lieut.-colonel, he was appointed head of a department dealing with the psychological aspects of military intelligence and subversive operations and was an adviser on scientific intelligence in Germany. After the war he returned to the Maudsley Hospital as senior physician and joined the staff of the Maida Vale Hospital for Nervous Diseases. In 1947 he was appointed to the chair of psychological medicine at Durham. He was also physician to the Royal Victoria Infirmary, Newcastle upon Tyne, and clinical director of psychiatric units in the regional mental health service. In 1949 he was elected F.R.C.P. He was appointed to the Edinburgh chair five years ago.

Even a formal biography shows that Kennedy was an unusual man who had an unusual career. Exactly how unusual and how effective is made clear only by the following memoirs from his friends.

I first met Alexander Kennedy in 1946 when he had returned to the Maudsley Hospital after an exciting, if not lurid, career in the Army. Thenceforth his adventures, his successes, and his life have been a never-failing source of pleasure to me. I have always come away from him feeling happier, amused, and more able to bear with the workaday world of psychiatry. It has been said that he told tall stories. Yet as I became closer to him, I found them confirmed on every side. Life was with him stranger than fiction, the result of his adventurous turn of mind and his zest for new experience. At one time a gambler on the Paris bourse in hectic post-war days, at another the familiar of desert sheikhs, sharing their mutton stews on the road to Mecca, yet again the author of immensely successful radio plays and member of the Brain's Trust of television—these were all roles Kennedy had played. He could do these things because there was about him a simple directness which brooked no awareness of "east nor west, border, nor breed, nor birth", which was his most [illegible]ing characteristic.

To see him purely as a doer would be entirely wrong, however, he had one of the best brains in psychiatry To examine with him, particularly if there was a good candidate, was a delight He was an accomplished lecturer, and his numerous papers are all marked by both clarity and learning But his learning was never recondite or produced for effect, it was a natural part of him He had built up one university department, and was busy building up the chair at Edinburgh when he died The peculiar problems inherent in the formation of a new, and yet major, department of medicine must ultimately depend for their solution on the character of the professor When the history of post-war psychiatry in Great Britain comes to be written, Kennedy will have an important place, for his work at Newcastle broke new ground He was the right man at the right time It is a tragedy that we cannot see his ideas further developed

D L

When Alexander Kennedy came to Newcastle as our first professor of psychological medicine, undergraduate instruction in psychiatry traditionally comprised a course of didactic lectures and an occasional dreary perambulation round the local mental hospital, mainly dedicated to the demonstration of a few cases of advanced insanity Of postgraduate education or research in psychiatry there was none When he left us for Edinburgh his successor inherited a highly organised, well-staffed, well-equipped, and vital department which had built up a fund of good will both within the medical school and outside it All this Alex achieved by a highly personal combination of sweet reasonableness, persuasion, bullying, horse-trading, and frank intrigue—which he relished During this short period Kennedy initiated a psychiatric consultative service of exemplary quality in the Royal Victoria Infirmary, as well as a splendid electroencephalographic department, and fathered the beginning of academic neurology as a separate discipline under his roof But he was active also in the region, where his enlightened energy furnished the motive power for a transformation of some of the most backward mental hospitals in the country into a group of institutions where patients could benefit fully from the current revolution in psychiatric treatment

These utilitarian preoccupations were a far cry from Flexner's initial conception of the role of the full-time clinical professor, but Kennedy had more excuse than most of his academic contemporaries for his absorption in organisation and administration to the virtual exclusion of personal research He found psychiatry in the dark ages, and until the machinery for its prosecution had been assembled it was useless to think in terms of technical development he was building for the future

As a teacher he was enormously popular—enthusiastic, histrionic, confidential, scandalous, and full of vivid illustrations drawn from his various and colourful experiences in the worlds of boxing, dirt-track riding, the Army, the Middle East, big business, the B B C , and that demimonde of psychopathy and drug addiction which clearly fascinated him as much as it did his listeners P it when he quietly gave his mind to a complicated clinical problem he was a most percipient diagnostician, with a flair for organic psychiatry And when his sympathies were engaged he was the kindest of doctors and the most understanding of men, often indeed manifesting a vein of indulgent soft-heartedness which contrasted strikingly with the braggadocio of his usual manner However, the fact that nobody could have looked less like a psychiatrist was undoubtedly one of his natural advantages, and under the influence of his robust bonhomie and astringent commonsense, even surgeons came to take account of his subject

Everything about Alexander Kennedy was larger than life—he was vital, passionate, ingenious, and infinitely versatile His chronic ill health, borne with bravery and humour, was known to all his friends, but his sudden loss was no less unexpected and tragic He was a most lovable man

H G M

Physically the large frame and characteristic walk of Alex edy was conspicuous in any company, and when we travelled as students on the London trams he was never charged a fare, for the conductor assumed he was a policeman in plain clothes He was outstanding as a fighter, boxing heavy-weight, and in a sense fighting was an essential part of his life, perhaps it had had to be When dirt-track racing was introduced, Alex paid some of his way through hospital with his earnings on the track. Despite these less conventional activities, he was a brilliant student and swept up most of the available medical prizes As a houseman, his fighting took the form of battling for various political causes, partly because of the opportunity for physical encounter they afforded He would get a telephone call while working in the laboratory and disappear to the East End, returning some hours later with fractured metacarpals, such heavy odds he enjoyed In the locust years and during the war I saw him only occasionally until he came to Edinburgh to the chair of psychological medicine "What will happen", one famous London physician is reported to have asked, "when an irresistible force meets an immovable object?" What did happen the colleagues in his own specialty can best say, but to the general physician what was so welcome was his ambition to integrate his specialty with the general medicine from which it has for too long been divorced and his readiness to forward any projects towards that end His memorial, and it is the only memorial he would have cared about, will be the realisation of his proposals for the place of psychological medicine in the Edinburgh of the future—a realisation he knew he would never see for himself For the rest of us, if we could capture but some of his zest for life, his tenacity of purpose, his humanity, and his own brand of special courage, we shall not do so badly

W I C

WILLIAM SCOTT PATTON

M B Edin

Dr W S Patton, emeritus professor of entomology in the University of Liverpool, died on May 26 at the age of 83

He was born at Hyderabad, the son of William Patton, J P, and was educated at Stokes School at Mussoorie He studied medicine at the Universities of Edinburgh and Marburg, and a year after he qualified in 1901 he joined the Indian Medical Service After spending some years with the Aden Boundary Commission studying malarial parasites, he was appointed to the King Institute of Preventive Medicine in Madras to carry out a special investigation into the ætiology of kala-azar Later he was promoted assistant director of the institute and undertook research into oriental sore During the 1914–18 war he served as entomologist to the Mesopotamian Expeditionary Force On demobilisation he worked as director of the Pasteur Institute at Coonoor In 1921 he moved to Edinburgh as lecturer in medical entomology, but three years later he returned to Asia when he was selected by the Royal Society as director of their kala-azar commission in Northern China In 1927 he was appointed to the chair of entomology in Liverpool, and he remained there till ill health forced him to retire in 1937 The following year he was awarded the Mary Kingsley medal of the Liverpool School of Tropical Medicine

Besides his classical studies on kala-azar and oriental sore Patton wrote on hæmogregarines, on the development of *Herpetomonas culicis*, a parasite of the mosquito, on a new piroplasm (*P gibsoni*) in foxhounds, on flagellates of the genera *Herpetomonas*, *Crithidia*, and *Rhynchoidomonas* (1912), and on the arthopods of medical and veterinary importance in Mesopotamia (1920) His *Textbook of Medical Entomology* with F W Cragg has been described as the *Debrett* of the entomological world ("If it is not in Patton it is not worth while")

P H M-B writes

"The name of W S Patton conjures up memories of a controversial figure He, almost more than anyone, was the father of modern tropical entomology His scientific output was stupendous and his zeal almost fanatical. I can see him still with blazing eyes and vigorous gestures at meetings of the Royal Society of Tropical Medicine in Chandos Street. There he held the stage and with oratory stirred and prodded the medical hierarchy in India into action. Patton was indeed part and parcel of India and the love of its people was in his blood. Despite opposition and criticism there can be no doubt that his considerable work on kala-azar eventually led to the final and conclusive victory by Shortt and his colleagues in 1942 and 1943."

On his retirement he lived in Devon, and he died in Bideford Hospital after a fall. He is survived by five sons and his widow, who contributed beautiful drawings to all his books.

JOHN INKSTER

M.D. Aberd., F.R.C.P., D.P.H.

Dr. Inkster, who died on June 15, was known and valued as a general physician in Middlesbrough and the North-East of England, where he was in consulting practice for nearly forty years.

He was born in Aberdeen in 1888 and was educated at the grammar school and university of the city. After qualifying in 1909 he held resident posts in London at Victoria Park Chest Hospital and at Great Ormond Street. During the 1914–18 war he served with the R.A.M.C. in France and Salonika. After his demobilisation with the rank of major he spent some time in postgraduate study, taking the M.R.C.P. in 1920, before settling in Middlesbrough. His work was centred on the North Ormesby Hospital, but he also served several other local hospitals as pathologist and physician. He was elected F.R.C.P. in 1941.

B. W., a colleague in Middlesbrough, writes:

"Dr. Inkster's work was quiet and unobtrusive, and he had few interests outside medicine, except for great enthusiasm for Freemasonry. He had very strong loyalties, especially to Aberdeen, the R.A.M.C., and the College of Physicians. He did much to make the changing-over at the time of the introduction of the National Health Service harmonious. He was also an early and keen supporter of the body which eventually became known as the Regional Hospitals Consultants' and Specialists' Association."

W. W. J., who qualified with him in Aberdeen in 1909, relates:

"We regarded, and treated, John Inkster as the baby of our class. He looked younger than most of us and in his rather precise way he retained his boyish appearance for most of his life. He was very gentle and deliberate in manner, never hurrying when answering a question but often quickly intervening to correct an inaccurate statement. He was a good friend, full of fun, and ever ready to see the humorous side of anything. Military service appealed to him, and he early joined the special reserve of officers, serving in the R.A.M.C. with distinction during the first world war. He was just as well-informed and meticulous in matters of military procedure as he was in matters medical, and no-one ever saw him improperly dressed when in uniform. Indeed in his early days he had his hair cut regularly at Truefitt's in Bond Street, which he regarded as the only place worthy of an officer's patronage. There was little prospect of his making a living in London so he moved to Middlesbrough, where Dickie, who was surgeon there, advised him there was need for a physician. And in Middlesbrough John Inkster spent nearly the whole of his professional life practising as a consulting physician and providing the standard of service one would expect from a man of his ability and high principle. His work kept him tied to the North Country but he often attended—and much enjoyed—the informal dinners at the Royal College of Physicians. He was a most lovable person who served his profession well."

Dr. Inkster is survived by his widow, two daughters, and a son who is a consultant anæsthetist in Newcastle upon Tyne.

Notes and News

SOMATIC WARDS IN MENTAL HOSPITALS

TOWARDS the end of 1958 an experiment was launched in the Swedish Ulleraker mental hospital about which Dr. N. B. Nordlander has a tale to tell.[1] Wards with 15 male and 15 female beds were equipped up to the standard of a modern general hospital and staffed by personnel trained to grapple with somatic as well as psychiatric ailments. These wards were visited by specialist surgeons and physicians, as well as by the hospital's psychiatric staff. Some of the patients had come from the psychiatric side of the hospital, having qualified for admission to one of the somatic wards by developing a somatic ailment such as pneumonia. Others had been admitted from without the hospital, again with some somatic complaint. Many were old folk whose physical disorders had triggered off mental disturbances. Operations, for example, had often had this effect, and the 210 men and 153 women cared for in these wards in 1959 included as many as 64 postoperative cases. The largest group (78 cases) was composed of patients presenting diagnostic problems—the case requiring a neurologist to discover some organic disease of the brain masquerading as insanity, the obscure case of anæmia, the possible cancer case, the victim of a nutritional disturbance, the patient with pyrexia of unknown origin, and so on. As many as 41 cases were listed as infections, and among these were nosocomial infections requiring special facilities for isolation. Cardiac decompensation was noted in 34 cases, and arteriosclerotic complications in 27. Delirium tremens accounted for 23 cases.

University of Cambridge

On Oct. 1 a Mary Marshall professorship of the physiology of reproduction and a professorship of chemical microbiology are to be established. Dr. A. S. Parkes, of the National Institute for Medical Research, London, has been appointed Mary Marshall professor and Dr. E. F. Gale director of the Medical Research Council chemical microbiology research unit at the University of Cambridge, professor of chemical microbiology. Both appointments are limited to one tenure.

On June 11 the following degrees were conferred:

M.D.—C. W. M. Adams, P. J. Dawson, H. B. Eckstein, R. W. Payne.
M.B., B.Chir.—George Willett (by proxy).
M.B.—D. R. F. Clark, R. B. Church.

University of London

Dr. H. Harris, reader in biochemical genetics at the London Hospital Medical College, has been appointed to the chair of biochemistry at King's College.

Dr. Harris, who is 40 years of age, was educated at Manchester Grammar School and the University of Cambridge, taking the degree of B.A. in 1941. After qualifying in 1943 he held a house-appointment at Sunderland Royal Infirmary. After his National Service in the R.A.F. medical service he spent 1947 to 1950 as an honorary research assistant at the Galton Laboratory of University College, London, while holding a Leverhulme scholarship of the Royal College of Physicians and a Lund fellowship of the Diabetic Association. In 1950 he was appointed to a lectureship at University College. Three years later he became senior lecturer in the department of biochemistry at the London Hospital Medical College and was appointed reader in 1958. His published work has mainly been concerned with the biochemical aspects of human genetics.

Mr. A. F. Huxley, reader in experimental biophysics in the University of Cambridge, has been appointed to the Jodrell chair of physiology at University College.

University of Wales

At recent examinations the following were successful:

D.P.H.—D. J. W. Anderson, J. N. Bodger, J. L. Davies, D. C. Drummond, C. E. Edwards, T. L. Jones, Peter Laws, P. C. Moore, I. D. G. Richards, Enid C. Vincent.

D.T.C.D.—Syed Zafar Ahmad, Bhalchandra Nilkanth Bhat, Sudarsan [illegible] Barua, Thakur Chakera, C. Chin Hin Chew, Dwarka Nath Gupta, Abdul Khaliq, Peter Macpherson, Maung Hla Maung, G. D. Murphy, Hari Anugrah Narain, Balasubramaniam Ponniah, Vijaya Chandra Rameshwar, Jamil Ahmad Siddiqui, Ibrahim Taha.

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[1] Svensk. Läkartidn. Mar. 13, 1960.

Royal College of Surgeons in Ireland

At a meeting of the college on June 7 the following officers were elected

President, T G Wilson, vice-president, N A Kinnear, council, R Atkinson Stoney, J F Devane, A A McConnell, T O Graham, A B Clery, Ian Fraser, T Millin, M P Burke, R R Woods, E N MacDermott, J H Coolican, D J Riordan, J G Mathews, J P Lanigan, F A J M Duff, D Montgomery, S T McCollum, J M McAuliffe Curtin, E O'Malley

On June 16 the fellowship of the college was conferred on the following

M T D Braide, J F Doyle, P B Kiely, Hosny Abd-el-Maksoud Mostafa, R W Pigott

Society of Apothecaries of London

On Tuesday, June 28, at 8 30 P M, Sir Tudor Thomas will be presented with the society's gold medal in therapeutics in recognition of his services to corneoplastic surgery

Royal Medical Foundation of Epsom College

The annual general meeting of the governors of Epsom College will be held at the Medical Defence Union, Tavistock House South, London, W C 1, on Wednesday, July 13, at 3 30 P M

World Medical Association

The General Assembly will be held in Berlin from Sept 16 to 22 Further particulars may be had from Bundesarztekammer-Kongressburo, Köln-Lindenthal, Haedenkampstr 1, Germany

International Symposium on Cori's Ester

This symposium will be held in Milan from Sept 16 to 18 under the presidency of Prof Carl Ferdinand Cori Further particulars may be had from the secretary of the organising committee, Via Modica, 6, Milan, Italy

Appeal against G M C Dismissed

On June 20 the judicial committee of the Privy Council dismissed Dr Kenneth Fox's appeal against the decision of the disciplinary committee of the General Medical Council ordering the erasure of his name from the Medical Register (see *Lancet*, 1959, ii, 1024)

World Standards for Protective Helmets

On the initiative of the British Standards Institution, the Protective Headwear Manufacturers Association, and other safety interests, a new committee of the International Standards Organisation has been set up to discuss world standards for the quality and testing of safety helmets The committee holds its first meeting at British Standards House in London from Oct 12 to 14

Restricting Medical Immigrants to U S.A

From July 1 graduates of medical schools in their own country will have to pass a test on medical knowledge and their grasp of the English language (*New York Times*, June 8, 1960) before they can obtain a hospital appointment in the United States At present they can either take the test at home or after arriving in the United States Some 3300 foreign medical graduates reach the United States each year, and it is expected that the new regulation will halve the number

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Mr John Boyd-Carpenter, Minister of Pensions and National Insurance, has asked the National Insurance Advisory Committee to consider four sets of draft regulations designed to implement their recent report on long-term hospital patients Representations should be sent in writing to the secretary of the committee, 10, John Adam Street, London, W C 2, not later than July 15

The Committee on the Problem of Noise, appointed by the Minister for Science, is now ready to receive evidence Anyone wishing to give evidence should first write to the committee's secretary, Mr R S Matthews, Ministry of Health, Savile Row, London,

Biochemical Society will hold a meeting on Wednesday and June 29 and 30, at 10 A M each day in the department of ry, University of Cambridge

Diary of the Week

JUNE 26 TO JULY 2

Monday, 27th

Postgraduate Medical School of London, Ducane Road, W 12
4 P M Dr Brian Ackner Aches and Pains of Psychogenic Origin

Wednesday, 29th

Royal Society of Medicine, 1, Wimpole Street, W 1
5 P M *Endocrinology* Dr John B Stanbury (Boston) Constitutional Factors in Thyroid Disease
Postgraduate Medical School of London
2 P M Dr R W Riddell Diseases Due to Fungi
Royal Free Hospital, Gray's Inn Road, W C 1
5 15 P M Dr Seymour S Kety (Bethesda) Current Biochemical Concepts of Schizophrenia
Institute of Dermatology, Lisle Street, W C.2
5 30 P M Dr Riddell Histopathology of Fungus Infection
Institute of Diseases of the Chest, Brompton, S W.3
5 P M Mr D S M Barlow Surgical Problems of Hiatus Hernia and Other Diaphragmatic Herniæ

Thursday, 30th

Postgraduate Medical School of London
4 P.M Dr J F Goodwin Rare Disorders of Heart Muscle
Institute of Dermatology
5 30 P.M Mr A K Monro Malignant Melanoma, Clinical and Pathological
Nuffield Orthopædic Centre, Oxford
8 30 P.M Dr Isidore Conn (Tulane) Rudolph Matas, the Pioneer of Vascular Surgery

Friday, 1st

Postgraduate Medical School of London
10 A M Prof John Bruce Cancer of the Breast

Saturday, 2nd

British Association of Allergists
10 A M (Wright-Fleming Institute, St Mary's Hospital, W 2) Short Papers

Appointments

Hargreaves, Elizabeth M, M.B Leeds, D P H assistant M O and school M O, Wetherby division, West Riding of Yorkshire
Kinnear, W F, M B St And, D O M S part-time consultant ophthalmologist, hospitals and school clinics, Scunthorpe, Gainsborough, and Brigg areas
Wild, David, M B Manc, D OBST, D P H senior M O, West Sussex
Wood, P R T, M B Lond assistant county and school M O, Horsham and Crawley areas, Sussex

Leeds Regional Hospital Board

Agnew, R A L, M D Dubl, M R C P I assistant psychiatrist (S H M O) Broadgate Hospital, Beverley
Ropschitz, D H, M D Genoa, D P M consultant in psychiatry, Storthes Hall Hospital, Huddersfield
Rosenthal, Leonard, M.D Leeds consultant in geriatrics, Wharfedale/Leeds area
Tupman, G S, M.B, B SC Manc, F R C S part-time consultant in orthopædic surgery, Scarborough, Bridlington, and Whitby areas

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